ncRNAimprint: A comprehensive database of mammalian imprinted noncoding RNAs

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ABSTRACT

Imprinted noncoding RNAs (ncRNAs) are expressed mono-allelically in a parent-of-origin-dependent manner, which is mainly evident in mammals. Lying at a crossroad between imprinted genes and ncRNAs, imprinted ncRNAs show distinct features. They are likely to function in nontraditional ways compared to non-imprinted ncRNAs, and are much more responsible for the mechanism of genomic imprinting compared to imprinted protein-coding genes. An increasing number of human diseases have been shown to be related to abnormalities in imprinted ncRNAs. Due to their functional importance, many studies focusing on imprinted ncRNAs have been published in recent years; however, there is no systematic collection or description of imprinted ncRNAs and the rapidly growing knowledge is scattered in various places. Here, we describe a new database, ncRNAimprint, which serves as a comprehensive resource center for mammalian imprinted ncRNAs. A catalog of imprinted ncRNAs, including snoRNAs, microRNAs, piRNAs, siRNAs, antisense ncRNAs, and mRNA-like ncRNAs, was annotated in detail using information extracted from relevant literature and databases. Comprehensive collections of imprinted ncRNA-related diseases, imprinting control regions (ICRs), and imprinted regions were manually compiled to provide resources for current research focusing on imprinted ncRNAs. Small RNA deep sequencing reads that fully matched within imprinted regions were also included to offer useful evidence in detecting novel imprinted ncRNAs and to aid in analyzing expression patterns of known imprinted ncRNAs. A search page including four effective search forms and two graphical browsers was created for rapid retrieval and visualization of these data. The imprinted ncRNA database is freely accessible at <http://rnaqueen.sysu.edu.cn/ncRNAimprint>.

Keywords: genomic imprinting; noncoding RNA; imprinted ncRNA; database

INTRODUCTION

Genomic imprinting is an epigenetic gene regulatory mechanism that results in mono-allelic gene expression in a parent-of-origin-dependent manner, which is mainly evident in placental mammals and flowering plants (Wood and Oakey 2006; Feil and Berger 2007). In mammals, imprinted genes include both protein-coding genes and noncoding RNAs (ncRNAs) (Morison et al. 2005; Royo and Cavaille 2008). At present, all known imprinted ncRNAs belong to the traditional categories of ncRNAs, including small nucleolar RNAs (snoRNAs), microRNAs (miRNAs), small interfering RNAs (siRNAs), Pivi-interacting RNAs (piRNAs), antisense ncRNAs, and mRNA-like ncRNAs (Seitz et al. 2004b; Peters and Robson 2008; Royo and Cavaille 2008;

Koerner et al. 2009). Imprinted ncRNAs lie at a crossroad between imprinted genes and ncRNA genes, with common and distinct features characteristic of both.

Functional characterizations reveal that imprinted ncRNAs are likely to function in nontraditional ways compared to their non-imprinted counterparts. For example, in vitro studies have shown that the snoRNA H/MBII-52 negatively regulates editing and alternative splicing of the serotonin 2C receptor (*5htr2c*) pre-RNA (Flomen et al. 2004; Vitali et al. 2005; Kishore and Stamm 2006; Doe et al. 2009), a function that differs completely from the traditional roles of snoRNAs in modifying ribosomal RNAs (rRNAs) or small nuclear RNAs (snRNAs) (Kiss 2002). In fact, other imprinted snoRNAs, such as H/MBII-85 and RBII-36, have unknown targets and are referred to as “orphan” snoRNAs (Seitz et al. 2004b). Similarly, imprinted miRNAs also engage in unexpected activities in mammals in which miRNAs function mostly by silencing their targets rather than by cleaving them, with no allele preference. Yet studies have shown that *antiPeg11*-hosted imprinted miRNAs display an allele-specific regulation of *Peg11*/ *Rtl1* in *trans* and guide

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cleavage of the *Peg11/Rhl1* mRNA due to the perfect complementary base-pairing between this miRNA and its target (Davis et al. 2005).

In addition, compared to imprinted protein-coding genes, imprinted ncRNAs show different imprinting features and are more responsible than imprinted protein-coding genes for the mechanism of genomic imprinting. It is imprinted ncRNAs, rather than protein-coding genes, that coexist with large imprinted regions and may contribute to the evolution and regulation of genomic imprinting. Evolutionary studies have indicated that most imprinted protein-coding genes are well conserved between species that use imprinting and species that do not use imprinting; however, examined imprinted ncRNAs are present only in organisms that use imprinting (Hore et al. 2007; Edwards et al. 2008; Nahkuri et al. 2008; Smits et al. 2008; Zhang and Qu 2009). A great deal of small imprinted ncRNAs, which cluster in imprinted regions and vary among mammals, were predicted to be associated with the acquisition and expansion of genomic imprinting (Glazov et al. 2008; Zhang and Qu 2009). Moreover, several imprinted antisense ncRNAs have been shown to be essential for mono-allelic silencing of flanking imprinted genes, and their transcription or they themselves may function as *cis*-restricted gene silencers in the regulation of imprinting (Pauler et al. 2007; Koerner et al. 2009).

Aside from ncRNAs, other important factors in the regulation of imprinting are imprinting control regions (ICRs), also referred to as ICEs (imprinting control elements), which display parent-specific DNA methylation established during gametogenesis and generally control the imprinting patterns of an entire imprinted region (Reinhart and Chaillet 2005; Edwards and Ferguson-Smith 2007). Certain ICRs function by collaborating with imprinted ncRNAs to establish and maintain normal expression pattern of flanking imprinted genes (Pauler et al. 2007; Koerner et al. 2009); however, abnormalities in imprinting patterns could cause serious diseases and disorders in species that use imprinting. Studies on the pathology of imprinting-related human diseases have demonstrated that imprinted ncRNAs play an important role. A growing number of human diseases, such as Prader-Willi syndrome (PWS), Beckwith-Wiedemann syndrome (BWS), Silver-Russell syndrome (SRS), transient neonatal diabetes mellitus (TNDM), and various tumors, has been shown to be related to certain imprinted ncRNAs (Blik et al. 2001; Temple and Shield 2002; Zhang et al. 2003; Blik et al. 2006; Sahoo et al. 2008).

Due to their functional significance, studies of imprinted ncRNAs are currently very active in both fields of genomic imprinting and ncRNA, and there has been a rapid accumulation of relevant knowledge in the past few years. Yet these data are scattered either throughout the literature or in various online databases. Although certain ncRNA records are included in databases of imprinted genes such as Geneimprint (<http://www.geneimprint.com/>), Catalog of Imprinted Genes (Morison et al. 2001), and WAMIDEX

(Schulz et al. 2008), many relevant annotations are insufficient and no discrimination is made between imprinted ncRNAs and protein-coding genes. As for databases that are focused on ncRNAs, such as snoRNABase (Lestrade and Weber 2006), miRBase (Griffiths-Jones et al. 2006), and NONCODE (Liu et al. 2005), information about imprinting features, including expressed allele, imprinted tissues and stages, ICRs and imprinted region, is rarely annotated. The condition of these databases makes it challenging for researchers who are focused on imprinted ncRNAs to quickly retrieve information that is relevant to their studies.

Another daunting challenge is to identify novel imprinted ncRNAs. At present, detection of imprinted ncRNAs, which is limited to several major imprinted loci and developmental stages in a few organisms, is far from sufficient. Functional characterizations are restricted to several particular examples and are not well generalized among mammalian imprinted ncRNAs, which is largely due to lack of support from adequate data. Therefore, genome-wide identification of imprinted ncRNAs in more species is required; however, this work is experimentally challenging because imprinted ncRNAs display tissue-, developmental stage-, and even species-specific expression patterns (Cavaille et al. 2000; Seitz et al. 2004b; Royo et al. 2007). More recently, deep sequencing technologies have been widely used to identify novel ncRNAs, which have led to the production of increasingly available sequencing data of small RNAs from diverse tissues and cell lines (Mardis 2008a; Mardis 2008b; Lister et al. 2009). An increasing number of bioinformatics tools has also been developed to explore these data (Friedlander et al. 2008; Langmead et al. 2009; Yang et al. 2010). Using these tools to analyze deep sequencing data would provide valuable evidence to detect novel imprinted ncRNAs.

Here we describe a database, ncRNAimprint, which integrates comprehensive information about mammalian imprinted ncRNAs. Three major sections of data were included: (1) a catalog of imprinted ncRNAs, with detailed annotation concerning imprinting features; (2) three comprehensive collections of imprinted ncRNA-related diseases, ICRs, and imprinted regions; and (3) deep sequencing reads that have been fully matched within known imprinted regions. To provide a simplified database structure, we classified all ncRNAs (including both experimentally validated and predicted data) into six categories according to their corresponding traditional families: snoRNAs, miRNAs, siRNAs, piRNAs, antisense ncRNAs, and mRNA-like ncRNAs. Each category was assigned detailed annotation fields to record information extracted from relevant literature and databases. In addition, three comprehensive collections were included to facilitate current research foci on (1) pathological roles of imprinted ncRNAs in related diseases; (2) functions of imprinted ncRNAs in the imprinting mechanism; and (3) evolutionary relationships between imprinted ncRNAs and the expansion of genomic imprinting. The currently available deep sequencing data of small

ncRNAs were also mapped to known imprinted regions, and fully matched reads were retained to provide helpful evidence in the identification of novel imprinted ncRNAs and to facilitate the examination of imprinted ncRNA expression patterns. Although the quantity of validated imprinted ncRNAs and relevant knowledge is presently limited, we believe abundant novel imprinted ncRNAs will be discovered, especially when the rapidly increasing deep-sequencing data and the ongoing completion of additional mammalian whole-genome sequences are considered. Moreover, by providing a centralized resource center, ncRNAimprint would facilitate wider detection and functional analysis of imprinted ncRNAs, and even help inspire novel ideas from researchers. The ncRNAimprint database will be constantly updated to keep pace with new studies and published data. The database is freely accessible at <http://rnaqueen.sysu.edu.cn/ncRNAimprint>.

RESULTS

A comprehensively annotated catalog of mammalian imprinted ncRNAs

ncRNAimprint has been designed to focus primarily on imprinted ncRNAs, which possess distinctive characteristics from both imprinted protein-coding genes and non-imprinted ncRNAs. Imprinted ncRNAs were collected and classified into six categories according to their previously defined families (snoRNAs, miRNAs, piRNAs, siRNAs, antisense ncRNAs, and mRNA-like ncRNAs). In addition, detailed annotations involving imprinting features were organized together in one web page per ncRNA entry. All known sequences can be batch downloaded using the “Download” page on the ncRNAimprint website.

Both validated and predicted data on imprinted ncRNAs were collected and imported into our database. Presently, ncRNAimprint contains data on imprinted ncRNAs from nine species, including human, rhesus, mouse, rat, cow, sheep, pig, wallaby, and opossum. Detailed statistics of each type of ncRNA in each species are listed in Table 1. Version 1.0 of the ncRNAimprint database contains 7253 ncRNAs, with predicted piRNAs making up the largest proportion of imprinted ncRNAs. Sequences of imprinted piRNAs and siRNAs were obtained by mapping predicted sequencing data to known imprinted regions (see Materials and Methods) without further experimental validation. Thus, current collections of all piRNAs and siRNAs are presented as predicted data. The other four categories (snoRNAs, miRNAs, antisense ncRNAs, and mRNA-like ncRNAs)

TABLE 1. Statistics of the ncRNAs available in the ncRNAimprint database

Species	snoRNA	miRNA	Antisense ncRNA	mRNA-like ncRNA	piRNA	siRNA	Total
Human	118	57	11	8	3748	0	3942
Rhesus	0	1	0	0	0	0	1
Mouse	120 ^a	127	13	11	2828	107	3206
Rat	86 ^b	0	0	2	0	0	88
Cow	0	0	0	4	0	0	4
Sheep	0	0	1	4	0	0	5
Pig	0	0	1	2	0	0	3
Wallaby	0	1	0	1	0	0	2
Opossum	0	1	0	1	0	0	2
Total	324	187	26	33	6576	107	7253

^aThe MBII-52 cluster accounts for 110 members (Nahkuri et al. 2008) and the MBII-85 cluster (Cavaille et al. 2000) accounts for only one because the predicted number of its members is uncertain. Both clusters were annotated as one record in the database.

^bThis sum is comprised of 86 copies of RBII-36 snoRNA in the RBII-36 cluster (Royo et al. 2007) which is annotated as one record in the database.

account for a total of 570 ncRNAs. The annotations of these families are, for the most part, validated because they were manually compiled and extracted from relevant literature and databases. The most widely available data are from humans and mice.

Imprinted ncRNAs can be browsed by using the “Browse” page (Fig. 1), where entries are displayed by ncRNA families. Each entry contains a dynamic link to its annotation page. A screenshot of one representative ncRNA annotation page is presented in Figure 2. Detailed annotations including imprinting features were compiled for each ncRNA category (Supplemental Table S1). In addition, category-specific annotation items, such as “overlapped sense gene” for antisense ncRNAs and “mature/miR* sequence” for miRNAs, were also assigned (Supplemental Table S1).

On the “Search” page, an effective search interface has been created and provided to search for imprinted ncRNAs. Detailed search fields are available for users to retrieve information using a variety of characteristics, including species, chromosome, name, ncRNA category, imprinting status, expressed allele, imprinted tissue, and other descriptive keywords. For example, researchers can obtain all maternally expressed imprinted miRNAs on mouse chromosome 12 by launching such a search, as shown in Figure 3.

A user-friendly graphical browser, MapView, which zooms and scrolls over chromosomes, was created to display the ncRNAs within imprinted regions of a genome (Fig. 2). The tracks of imprinted ncRNAs and regions contain dynamic links to relevant annotation pages, where links to “MapView” are also available (Fig. 2). Organisms and regions can be selected from the forms as queries, or standardized chromosomal positions can be entered. With this tool, researchers can conveniently examine imprinted ncRNAs that are clustered, overlapping, or located in the same imprinted region.

Browse ncRNAs in ncRNAimprint

All ncRNAs microRNAs snoRNAs antisense ncRNAs mRNA-like ncRNAs ▼ piRNAs siRNAs							
30 Records for Each Page Display Page : 1 [Record 1 ~ 30] Total: 33 Records.							
Name	Aliases	Organism ▲	Chromosome	Position	Status	Expressed Allele	Update
bta-MEG3	GTL2	<i>Bos taurus</i>	21		Imprinted	Maternal	2009-05-21
bta-ITUP1	MIM1, MIMT1, IMPO1	<i>Bos taurus</i>	18		Imprinted	Paternal	2009-05-23
bta-H19		<i>Bos taurus</i>	29	51364542-51366914	Imprinted	Maternal	2009-05-23
bta-XIST		<i>Bos taurus</i>	X	47180022-47216556	Imprinted	Paternal	2009-05-20
hsa-HYMAI	NCRNA00020, PLAGLE	<i>Homo sapiens</i>	6	144365728-144371560	Imprinted	Paternal	2009-05-24
hsa-INPP5F_V2	SAC2_V2, KIAA0966_V2, hSac2_V2	<i>Homo sapiens</i>	10		Imprinted	Paternal	2009-05-22
hsa-MEG3	GTL2, FP504, prebp1, PRO0518, PRO2160, FLJ31163, FLJ42589, NCRNA00023	<i>Homo sapiens</i>	14	100362216-100397121	Imprinted	Maternal	2009-05-21
hsa-ITUP1	MIM1, MIMT1, IMPO1	<i>Homo sapiens</i>	19		Imprinted	Paternal	2009-05-23
hsa-GNAS-Exon 1A	exon 1A, exon A/B	<i>Homo sapiens</i>	20		Imprinted	Paternal	2009-05-23
hsa-MEG8	NCRNA00024	<i>Homo sapiens</i>	14	100430860-100443058	Provisional	Unknown	2009-05-21
hsa-XIST	XCE, XIC, SX11, swd56, DXS1089, DXS399E, DKFZp779P0129	<i>Homo sapiens</i>	X	72957220-72989313	Not Imprinted	The inactive X chromosome	2009-05-20
hsa-H19	D11S813E, ASM, ASM1, NCRNA00008, BWS, MGC4485, PRO2605, D11S813E	<i>Homo sapiens</i>	11	1972982-1975641	Imprinted	Maternal	2009-05-23
meu-H19		<i>Macropus eugenii</i>			Imprinted	Maternal	2009-05-23
mdo-H19		<i>Monodelphis domestica</i>			Imprinted	Maternal	2009-05-23

FIGURE 1. A screenshot of the webpage designed to browse for imprinted ncRNAs.

Comprehensive collections: Related diseases, ICRs, and imprinted regions

Studies regarding imprinted ncRNAs mostly concern (1) pathology of imprinted ncRNA-related diseases; (2) imprinting mechanisms; (3) evolution of imprinted ncRNAs and their relationship to the origin and expansion of genomic imprinting; and (4) identification of novel imprinted ncRNAs. In order to provide comprehensive information to facilitate these studies, four categories were organized and imported into ncRNAimprint: imprinted ncRNA-related diseases, ICRs, imprinted regions, and deep sequencing data. In this section, collections of diseases, ICRs, and imprinted regions will be introduced. Statistics summarizing these data are listed in Table 2.

A single imprinted ncRNA can be responsible for several disorders; however, single diseases could be associated with multiple ncRNAs. A detailed organization of these complex relationships is necessary for further studies on pathological roles of imprinted ncRNAs. By extracting information from publications and relevant databases, we established a collection of disease–ncRNA relationships in ncRNAimprint. Currently, 127 records are included, and each record represents a single relationship between one ncRNA and one disease. A special search interface for imprinted ncRNA-related diseases was created and is presented on the “Search” page. By launching a query, users can easily retrieve all disorders related to one imprinted ncRNA (Fig. 4), or all

ncRNAs relevant to a certain disease. A full list of disease–ncRNA relationships is able to be downloaded from the “Download” page and can be browsed by using the “Browse” function on the website (Fig. 5).

ICRs are important controllers of imprinting patterns over entire imprinted domains (Reinhart and Chaillet 2005; Edwards and Ferguson-Smith 2007), which influence the expression of imprinted ncRNAs. In addition, studies have demonstrated that imprinted ncRNAs participate in imprinting regulation, and some ncRNAs function by interacting with ICRs (Pauler et al. 2007; Koerner et al. 2009). As a result, a collection of ICRs is also crucial and helpful for studying regulatory roles of imprinted ncRNAs. We extracted the scattered information on ICRs from research papers, and 15 records were obtained. These data can be retrieved from the “Search,” “Browse,” (Fig. 5) or “Download” pages of ncRNAimprint.

Evolutionary studies of imprinted regions indicate that imprinted ncRNAs are more responsible for the origin and evolution of genomic imprinting than imprinted protein-coding genes (see Introduction); however, current evolutionary analyses of both imprinted ncRNAs and imprinted regions are limited to several well known examples (Paulsen et al. 2005; Edwards et al. 2008; Glazov et al. 2008; Nahkuri et al. 2008; Smits et al. 2008; Zhang and Qu 2009). To undertake broader studies of more imprinted regions, a full list of known imprinted regions becomes necessary. Therefore, ncRNAimprint includes a catalog of imprinted regions.

hsa-H19

ncRNAimprint MapView on Human Mar. 2006 Assembly

Position: chr11:1972982-1975641 **Size:** 2660bp **Genome:** Human **View** **Region:** ---

Zoom in: 1.5 X 3 X 10 X **Zoom out:** 1.5 X 3 X 10 X **Move:** <<10000 <<500 <<50 50>>

Chromosome 11

chr11: |1972982 |1973426 |1973870 |1974314 |1974758 |1975202

hsa-11p15

hsa-mir-675

hsa-H19

Imprinted Regions

snoRNAs

microRNAs

antisense ncRNAs

mRNA-like ncRNAs

piRNAs

siRNAs

Description:

H19 is a maternally expressed non-coding RNA. It functions in tumor suppression and oncogenesis, particularly in breast cancer. Mutations in this gene are associated with Beckwith-Wiedemann Syndrome and Wilms tumor. H19 also play a role in transcriptional and posttranscriptional regulation.

Sequence: [hsa-H19 sequence](#)

Links: [UCSC](#) [Gene](#) [Pubmed](#)

[1] Yu, L., Chen, M., Zhao, D., Yi, P., Lu, L., Han, J., Zheng, X., Zhou, Y. and Li, L. (2009) The H19 Gene Imprinting in Normal Pregnancy and Pre-eclampsia. *Placenta*, 30, 443-447.

[2] Bruce, S., Hannula-Jouppi, K., Peltonen, J., Kere, J. and Lipsanen-Nyman, M. (2009) Clinically distinct epigenetic subgroups in Silver-Russell syndrome: the degree of H19 hypomethylation associates with phenotype severity and genital and skeletal anomalies. *J Clin Endocrinol Metab*, 94, 579-587.

[3] Yamazawa, K., Kagami, M., Fukami, M., Matsubara, K. and Ogata, T. (2008) Monozygotic female twins discordant for Silver-Russell syndrome and hypomethylation of the H19-DMR. *J Hum Genet*, 53, 950-955.

[4] Smits, G., Mungall, A.J., Griffiths-Jones, S., Smith, P., Beury, D., Matthews, L., Rogers, J., Pask, A.J., Shaw, G., VandeBerg,

FIGURE 2. A screenshot of the annotation page for one imprinted ncRNA showing the link to the graphical browser, “MapView.” A human imprinted ncRNA, H19, is presented as an example.

Unfortunately, due to the small amount of available data from other species, only human and mouse data were compiled. In total, 72 entries were obtained. These data can be obtained using the “Search”, “Browse” (Fig. 5), or “Download” pages of ncRNAimprint. In addition, all included ncRNAs in each imprinted region can be viewed in the graphical browser “MapView” (Fig. 2).

Involvement of deep sequencing data

The identification of novel imprinted ncRNAs is an important part of present studies and further progress in this field. Both the generalization of functional characterizations of imprinted ncRNAs and comprehensive evolutionary analyses rely greatly on a sufficient number of experimentally validated imprinted ncRNAs. Yet, these data are far from adequate, even in known imprinted regions. A global survey of genomic imprinting in mice using deep

sequencing reveals a large fraction of novel ncRNAs might reside within known imprinted loci (Babak et al. 2008).

We downloaded deep sequencing reads of small ncRNAs from Gene Expression Omnibus (GEO) in the National Center for Biotechnology Information (NCBI) database (Barrett et al. 2009) and mapped them to imprinted regions in the human and mouse genomes to obtain fully matched reads (see Materials and Methods). These results were imported into our database and are displayed graphically on the website using the “DeepMap” browser (Fig. 6). This graphical interface is a helpful tool to examine expression patterns of known imprinted ncRNAs and novel ones. For example, as shown in Figure 6, the abundance track of reads that overlap with mmu-mir-379 reveals the expression features of this miRNA. The upper red block indicates the abundance of the mature miRNA, miR-379, while the lower block represents the degraded strand of the pre-miRNA. This observation applies to most miRNAs, which

A
Search for ncRNAs

Species: contains Mouse

Chromosome: contains 12

Name: contains

Category: microRNA

Status: contains Imprinted

Expressed Allele: contains Maternal

Imprinted Tissue: contains [eg: brain,placenta,liver...]

Disease: contains

Description Word: contains [eg: name,phenotype,disease...]

Date Last Update: after [eg: yyyy-mm-dd]

B
ncRNA Search Result

11 Records Found

30 Records for Each Page. Page : 1 [Record 1 ~ 11]

Name	Aliases	Organism ▲	Chromosome	Position	Status	Expressed Allele	Update
mmu-mir-337	microRNA 337, mir 337	<i>Mus musculus</i>	12	110823999-110824095	Imprinted	Maternal	2009-06-01
mmu-mir-431	microRNA 431, mir 431	<i>Mus musculus</i>	12	110828657-110828747	Imprinted	Maternal	2009-06-01
mmu-mir-127	microRNA 127, Mir127	<i>Mus musculus</i>	12	110831056-110831125	Imprinted	Maternal	2009-05-30
mmu-mir-136	microRNA 136, Mir136	<i>Mus musculus</i>	12	110833537-110833598	Imprinted	Maternal	2009-06-01
mmu-mir-370	microRNA 370, mir 370	<i>Mus musculus</i>	12	110856468-110856546	Imprinted	Maternal	2009-06-01
mmu-mir-411	microRNA 411, mir 411	<i>Mus musculus</i>	12	110948385-110948466	Imprinted	Maternal	2009-06-01
mmu-mir-380	microRNA 380, mir 380	<i>Mus musculus</i>	12	110950013-110950073	Imprinted	Maternal	2009-06-01
mmu-mir-376b	microRNA 376b, mir 376b	<i>Mus musculus</i>	12	110961688-110961749	Imprinted	Maternal	2009-06-01
mmu-mir-134	microRNA 134, Mir134	<i>Mus musculus</i>	12	110972349-110972419	Imprinted	Maternal	2009-05-31
mmu-mir-154	microRNA 154, Mir154	<i>Mus musculus</i>	12	110976543-110976708	Imprinted	Maternal	2009-05-31
mmu-mir-410	microRNA 410, mir 410	<i>Mus musculus</i>	12	110981925-110982005	Imprinted	Maternal	2009-05-31

FIGURE 3. An example of the search interface for retrieving imprinted ncRNAs. (A) A screenshot of the search interface used to retrieve imprinted ncRNAs. In the query form, items can be selected to retrieve “all maternally expressed imprinted miRNAs on mouse chromosome 12.” (B) A screenshot of the corresponding search result.

could be used to predict novel miRNAs in areas where similar patterns appear in the genome. The software for identifying miRNAs from deep sequencing data, miRDeep, has also integrated this concept in its design (Friedlander et al. 2008).

DISCUSSION

A comprehensive resource center for imprinted ncRNA

We developed a database, ncRNAimprint, which houses a manually curated catalog of mammalian imprinted ncRNAs, as well as comprehensive collections of imprinted ncRNA-related human diseases, ICRs, and imprinted regions. We classified all ncRNAs according to their traditional families and annotated them in detail, which would provide a clearer picture of the characteristics of imprinted ncRNAs and useful data resources for researchers. For example, the collection of imprinted miRNAs could serve as helpful data to identify novel imprinted miRNAs in other organisms, or to analyze origin and evolution of

imprinted miRNAs. By searching paralogs miRNAs of imprinted miRNAs from database miRBase (Griffiths-Jones et al. 2006), we have obtained a great number of novel imprinted miRNA candidates for further analysis (data not shown). Moreover, the three comprehensive collections of diseases, ICRs, and imprinted regions would facilitate current research foci. For instance, using the ncRNAimprint database, researchers can analyze the evolution of genomic imprinting on an unprecedentedly universal scale, including all mammals and even other species that have fully sequenced genomes. Using both imprinted regions and ncRNAs as queries to retrieve sequences of syntenic loci and paralogs from these genomes would provide valuable raw data for further evolutionary studies. Novel candidates

TABLE 2. Statistics of three comprehensive collections

Species	Related disease	ICR	Imprinted region	Total
Human	127	7	36	170
Mouse	0	8	36	44
Total	127	15	72	214

A

Search for Diseases

Species: [eg: Human, Hs, Homo sapiens, ...]
Name: [eg: Beckwith-Wiedemann syndrome (BWS), ovarian cancer, ...]
Associated ncRNA: [eg: H19, hsa-miR-127, HYMAI ...]
Associated Region: [input region locus, eg: 14q32, 11p15, 6q24.2 ...]
OMIM Number: [eg: 103280, 603233, 605636 ...]
Description Word: [eg: name, phenotype, disease ...]
Date Last Update: [eg: yyyy-mm-dd]

B

Disease Search Result

4 record found

Records for Each Page. Page: [Record 1 ~ 4]

Name ▲	Alias	Organsm	Associated ncRNA	Update
Beckwith-Wiedemann syndrome (BWS)	Wiedemann-Beckwith syndrome (WBS), Exomphalos - macroglossia - gigantism syndrome(EMG syndrome)	<i>Homo sapiens</i>	hsa-H19	2009-03-29
Hemihyperplasia (HHP)	Herni 3 syndrome, Hemihypertrophy	<i>Homo sapiens</i>	hsa-H19	2009-06-20
Silver-Russell syndrome (SRS)	Silver-Russell dwarfism, Russell-Silver syndrome (RSS)	<i>Homo sapiens</i>	hsa-H19	2009-06-20
Wilms tumor		<i>Homo sapiens</i>	hsa-H19	2009-06-10

FIGURE 4. An example of the search interface for retrieving imprinted ncRNA-related diseases. (A) A screenshot of the search interface used to query for diseases related to imprinted ncRNAs. In the query form, certain items are selected for retrieving “all human diseases related to H19.” (B) A screenshot of the corresponding search result.

of imprinted regions and ncRNAs might be predicted by exploring these data.

In addition, by an exhaustive retrieval and organization of data, we have made two important discoveries that might have been previously overlooked by researchers of imprinted ncRNAs. First, by downloading miRNA tracks located within imprinted regions from the UCSC Table Browser (<http://genome.ucsc.edu/>; Rhead et al. 2010), we found a large cluster of miRNAs (Fig. 7) present in one intron of the mouse imprinted gene, *Scn-like* with four mbt domains 2 (*Sfmbt2*) (Kuzmin et al. 2008). In total, 65 miRNA copies (40 different miRNAs) were included in this cluster, which, to date, would be the largest known miRNA cluster located in an imprinted region; however, no research paper or review has noticed this *Sfmbt2*-hosted miRNA cluster because its miRNA members were detected by several different studies. Basic genomic features of the cluster are shown in Figure 7. Similar to another large imprinted miRNA cluster, the mir-379/mir-656 cluster (Seitz et al. 2004a; Glazov et al. 2008), certain location patterns of *Sfmbt2*-hosted miRNAs suggest an evolution process by tandem duplication of an ancient precursor sequence or, more likely, of several sequences as a group (Fig. 7A). Members of this cluster belong to two miRNA families according to miRBase (Griffiths-Jones et al. 2006), mmu-mir-466 and mmu-mir-467. The latter one could be divided into four subfamilies: mmu-mir-297,

mmu-mir-467, mmu-mir-466, and mmu-mir-669. T-Coffee (version 8.69; Notredame et al. 2000) alignment results reveal the members of each family are well conserved (Fig. 7B), but members from different families/subfamilies show high diversity (data not shown). By analyzing genomic sequence and deep sequencing data, we found no miRNA candidate in the syntenic region of human, suggesting this cluster is rodent- and even mouse-specific. Whether possible counterparts of this cluster are present in rat is under study. This species-specific feature is distinct from the mir-379/mir-656 cluster, which is relatively well conserved among human, mouse, and rat (Glazov et al. 2008). Several aspects of this cluster should be examined further, such as whether this cluster is present in other species, whether this cluster is located in a larger imprinted region that includes genes in addition to *Sfmbt2*, whether this cluster coexists with the imprinting expression of *Sfmbt2*, and the function, expression, and imprinting patterns of the miRNAs within this cluster.

Second, we found that one mouse box H/ACA snoRNA, ACA54, is hosted by an imprinted gene, the nucleosome assembly protein 1-like 4 (*Nap1l4*) (Engemann et al. 2000; Umlauf et al. 2004). The current prevailing viewpoint is that imprinted snoRNAs include only C/D RNAs because no H/ACA box RNA has been found to be imprinted (Seitz et al. 2004b; Royo and Cavaille 2008). Apparently, this potentially imprinted H/ACA snoRNA has been ignored.

ncRNAimprint

Home Information Search Browse MapView DeepMap Statistics Download Links Help

Browse
ncRNA
disease
imprinted region
ICR

Disease Search Result

27 record found

30 Records for Each Page. Display Page: 1 [Record 1 ~ 30]

Name ▲	Alias	Organism	Associated ncRNA	Update
acute lymphoblastic leukemia (ALL)		Homo Sapiens	hsa-miR-335	2009-06-20
acute myeloid leukemia (AML)		Homo Sapiens	hsa-miR-335	2009-06-20
acute promyelocytic leukemia (APL)		Homo Sapiens	hsa-miR-134	2009-06-20

Region Search Result

72 Records Found

30 Records for Each Page. Display Page: 1 [Record 1 ~ 30]

ID	Alias	Organism ▲	Chromosome	Position	Update
hsa-1p31		Homo sapiens	1	68284233-68289069	2009-05-26
hsa-1p36		Homo sapiens	1	3558989-3640327	2009-05-26

ICR Search Result

15 record found

30 Records for Each Page. Display Page: 1 [Record 1 ~ 15]

ID	Alias	Organism ▲	Chromosome	Position	Methylated Allele	Update
hsa-7q21.3-IC1		Homo sapiens	7			2009-05-26
hsa-15q11-q13-IC1	PWS-IC	Homo sapiens	15	SNRPN promoter and exon 1	Maternal	2009-05-25
hsa-15q11-q13-IC2	AS-IC	Homo sapiens	15	~35 kb upstream of SNRPN	Maternal	2009-05-25
hsa-6q24.2-IC1	HYMAI/PLAGL1-IC, HYMAI/PLAGL1-DMR	Homo sapiens	6	exon 1 of HYMAI/PLAGL1	Maternal	2009-05-26
hsa-11p15-IC1	H19/IGF2-ICR, H19/IGF2-DMR	Homo sapiens	11	between H19 and IGF2	Paternal	2009-05-25
hsa-11p15-IC2	KvDMR1, KCNQ1-ICR	Homo sapiens	11	intron of KCNQ1	Maternal	2009-05-25
hsa-14q32-IC1	DLK1/DIO3 ICR, DLK1/DIO3 IG-DMR, DLK1-GTL2-IG-DMR	Homo sapiens	14	upstream of GTL2	Paternal	2009-05-26
mmu-17qA1-IC1	Igf2r/Air-ICR, Air-DMR	Mus musculus	17	intron 2 of Igf2r	Maternal	2009-05-26
mmu-7qF5-IC2	KvDMR1, Kcnq1-ICR	Mus musculus	7	intron 10 of Kcnq1	Maternal	2009-05-25
mmu-2qH3-qH4-ICR2	Exon 1A-ICR, Exon 1A-DMR	Mus musculus	2	Exon 1A promoter	Maternal	2009-05-25
mmu-2qH3-qH4-ICR1	Gnasxl-Nespas-DMR, Gnasxl-Nespas-ICR	Mus musculus	2	Gnasxl and Nespas promoters	Maternal	2009-05-25
mmu-7qC-IC1	PWS-IC	Mus musculus	7	Snrpn promoter and exon 1	Maternal	2009-05-25
mmu-10A-IC1	Hymai/Plagl1-IC, Hymai/Plagl1-DMR	Mus musculus	10	exon 1 of Hymai/Plagl1	Maternal	2009-05-25
mmu-7qF5-IC1	H19/Igf2-ICR, H19/Igf2-DMR	Mus musculus	7	between H19 and Igf2	Paternal	2009-05-25

FIGURE 5. A screenshot showing three web pages designed to browse for imprinted ncRNA-related diseases, imprinted regions, and ICRs. Each “Name” item has a link to its relevant annotation page.

Unlike other imprinted snoRNAs that are devoid of traditional targets, this snoRNA is predicted to guide the pseudouridylation of 28S rRNA U3801 (Schattner et al. 2006). In addition, according to the alignment result presented by snoRNABase (Lestrade and Weber 2006), this snoRNA is well conserved among vertebrates.

As exemplified by the two cases above, ncRNAimprint provides a centralized comprehensive resource center for studies concerning imprinted ncRNAs. In addition, the database will be regularly updated according to newly published data in order to present up-to-date information.

Deep Sequencing Data Map on Imprinted Regions [Mouse July 2007 Assembly]

FIGURE 6. A screenshot of “DeepMap” browser.

Detection of novel imprinted ncRNAs from deep sequencing data

As discussed above (see Introduction), mapping deep sequencing data to known imprinted regions could provide valuable information, not only for analyzing expression patterns of known imprinted ncRNAs, but also in detecting

novel noncoding transcripts in these loci. Although most of these data have been explored on a whole genome scale that already includes imprinted regions, relevant studies paid little attention to examining imprinted regions. As a result, valuable data about imprinted ncRNAs might be ignored or filtered out. For example, the miRNA members of *Sfnbt2*-hosted miRNA cluster (see Discussion, above) were actually

detected in several different studies that were not focused on whether the newly identified miRNAs are imprinted or not. Therefore, this cluster was easily overlooked. Furthermore, by analyzing deep sequencing data we have obtained a set of miRNA candidates present within imprinted regions (data not shown). The graphical browser, Deep-Map, which was created to show the tracks of fully matched deep sequencing reads in human and mouse imprinted regions, can provide helpful clues to identify novel non-coding transcripts in certain imprinted regions. In addition, researchers can also download the sequences of imprinted regions from ncRNAimprint, and map deep sequencing reads of their concerned libraries to these regions. To account for the rapid accumulation of available data, we will regularly update our database to ensure the inclusion of newly published deep sequencing data and novel imprinted regions.

MATERIALS AND METHODS

Data collection and detailed annotations

An exhaustive search for reviews of imprinted ncRNAs was performed using queries from a table of keywords, including, but not limited to, “ncRNA,” “genomic imprinting,” “noncoding,” and “imprinted.” A catalog including ncRNA name and organism was compiled based on analyses of these reviews and their cited references. For each ncRNA, we extracted annotations, references, and sequences by performing comprehensive searches in relevant databases (Supplemental Table S2). Imprinting features, such as imprinted region, imprinted tissues and stages, ICRs and expressed allele, which could not be found in existing databases, were obtained by analyzing related publications. The compiled annotations were then formalized and automatically imported into a MySQL database with tables for four ncRNA categories: snoRNAs, miRNAs, antisense ncRNAs, and mRNA-like ncRNAs. Each table was assigned general annotation fields, as well as specific annotation fields for its corresponding category (Supplemental Table S1).

Annotations for imprinted ncRNA-related diseases, ICRs, and imprinted regions were also obtained by analyzing literature and extracting data from relevant databases (Supplemental Table S2). Most information about imprinted ncRNA-related ncRNAs was collected from the Online Mendelian Inheritance in Man (OMIM) (<http://www.ncbi.nlm.nih.gov/omim/>) and miR2Disease (only for miRNAs) (Jiang et al. 2009) databases, using ncRNA names or aliases as queries. A collection of ICRs was mainly extracted from research papers, and a summary table of mammalian imprinted genes was downloaded from the Catalog of Imprinted Genes (Morison et al. 2001). From this table, the beginning and end of each imprinted region were defined as the first and last gene,

respectively, that are known to be imprinted at that location. Only data from the human and mouse regions were collected. Sequences were downloaded from the human (Mar. 2006; NCBI36/hg18) and mouse (July 2007; NCBI37/mm9) assemblies using the UCSC Genome Browser (Rhead et al. 2010). Annotations of diseases, ICRs, and imprinted regions were manually compiled and imported respectively into three separate tables in the MySQL database.

To add newly detected miRNAs and snoRNAs that may not be included in any review about imprinted ncRNAs, tracks of snoRNAs and miRNAs in all imprinted regions were downloaded from the UCSC Table Browser (<http://genome.ucsc.edu/>; Rhead et al. 2010). Human sno/miRNA tracks were downloaded from the human (Mar. 2006; NCBI36/hg18) assembly. Mouse miRNA tracks were downloaded from the mouse (July 2007; NCBI37/mm9) assembly.

Deep sequencing data processing

A total of 69 small-RNA libraries of diverse tissues and cell lines from human and mouse were compiled from nine related studies (Supplementary Table S2) and downloaded from the NCBI GEO website (Barrett et al. 2009). Three predicted piRNA data sets (accession numbers: DQ569913–DQ601958; DQ539889–DQ569912; AB349185–AB353040) and one oocyte clustered small RNA data set (accession numbers: AB334800–AB349184) were downloaded from the NCBI Genbank database (Benson et al. 2008). The reads with 3' adapters or barcodes were truncated to remove these sequences using our in-house Pascal scripts. Reads without adapters in each library were mapped to human and mouse imprinted regions, using Bowtie (version 0.9.9.3; Langmead et al. 2009) with options: `-f -k 200 -v 0`. Only reads that matched over their entire length were retained for import into our MySQL database.

SUPPLEMENTAL MATERIAL

Supplemental material can be found at <http://www.rnajournal.org>.

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FIGURE 7. Basic genomic features of mouse *Sfnbt2*-hosted miRNA cluster. (A) Location patterns of the cluster members (drawn to scale). The chromosomal region of the cluster is chr2: 10,388,571–10,439,906 (July 2007; NCBI37/mm9). All 65 miRNA copies are included, and each miRNA is indicated by an abbreviated symbol of its name (e.g., mmu-mir-466f-1 is denoted by 466f-1). Several repeats of similar patterns (such as “467c, 466b-1, 669a-3” and “467a, 466b-1”) suggest tandem duplications during expansion of the cluster. (B) T-Coffee (Notredame et al. 2000) alignments of miRNA families in the cluster. Five alignments are presented for the mmu-mir-466 family and four subfamilies of the mmu-mir-467 family, including mmu-mir-297, mmu-mir-466, mmu-mir-467, and mmu-mir-669.

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