ncRNA2MetS: a manually curated database for non-coding RNAs associated with metabolic syndrome

6   Dengju Yao[1, 2, 3], Xiaojuan Zhan[4, 5], Xiaorong Zhan[6], Chee Keong Kwoh[2], Yuezhongyi Sun[1, 5]

8   [1] School of Software and Microelectronics, Harbin University of Science and Technology,
9   Harbin, Heilongjiang, China
10 [2] School of Computer Science and Engineering, Nanyang Technological University, Singapore
11 [3] College of Bioinformatics Science and Technology, Harbin Medical University, Harbin,
12 Heilongjiang, China
13 [4] College of Computer Science and Technology, Heilongjiang Institute of Technology, Harbin,
14 Heilongjiang, China
15 [5] School of Computer Science and Technology, Harbin University of Science and Technology,
16 Harbin, Heilongjiang, China
17 [6] Department of Endocrinology and Metabolism, the First Affiliated Hospital of Harbin Medical
18 University, Harbin, Heilongjiang, China

19

20 Corresponding Author:
21 Dengju Yao
22 Harbin, Heilongjiang, China
23 Email address: ydkvictory@hrbust.edu.cn

24

Abstract

26 Metabolic syndrome is a cluster of the most dangerous heart attack risk factors (diabetes and
27 raised fasting plasma glucose, abdominal obesity, high cholesterol and high blood pressure), and
28 has become a major global threat to human health. A number of studies have demonstrated that
29 hundreds of non-coding RNAs, including miRNAs and lncRNAs, are involved in metabolic
30 syndrome-related diseases such as obesity, type 2 diabetes mellitus, hypertension etc. However,
31 these research results are distributed in a large number of literature, which is not conducive to
32 analysis and use. There is an urgent need to integrate these relationship data between metabolic
33 syndrome and non-coding RNA into a specialized database. To address this need, we developed
34 a metabolic syndrome-associated non-coding RNA database (ncRNA2MetS) to curate the
35 associations between metabolic syndrome and non-coding RNA. Currently, ncRNA2MetS
36 contains 1068 associations between five metabolic syndrome traits and 627 non-coding RNAs
37 (543 miRNAs and 84 lncRNAs) in four species. Each record in ncRNA2MetS database
38 represents a pair of disease-miRNA (lncRNA) association consisting of non-coding RNA
39 category, miRNA (lncRNA) name, name of metabolic syndrome trait, expressive patterns of

40 non-coding RNA, method for validation, specie involved, a brief introduction to the association,
41 the article referenced, etc. We also developed a user-friendly website so that users can access and
42 download all data easily. In short, ncRNA2MetS is a complete and high-quality data resource
43 for exploring the role of non-coding RNA in the pathogenesis of metabolic syndrome and
44 seeking new treatment options. The website is freely available at http://www.biomed-
45 bigdata.com:50020/index.html
46

Introduction

48 Metabolic syndrome (MetS) is a cluster of the most dangerous heart attack risk factors: diabetes
49 and raised fasting plasma glucose, abdominal obesity, high cholesterol and high blood pressure
50 (Alberti et al., 2005). It is estimated that around 20-25% of the world's adult population have
51 metabolic syndrome, making them three times more likely to have, and twice as likely to die
52 from, a heart attack or stroke when compared to people without the syndrome (International
53 Diabetes Federation, 2006). Metabolic syndrome has become a major threat to human health
54 around the world. However, to date, the pathogenesis of metabolic syndrome continues to
55 challenge experts. In recent years, a growing number of studies have suggested that many non-
56 coding RNAs (ncRNAs), including small non-coding RNAs, particularly microRNAs (miRNAs),
57 and long non-coding RNAs (lncRNAs), may be involved in metabolic syndrome-related diseases
58 such as obesity, type 2 diabetes mellitus, hypertension etc. (Stoll et al., 2018; Sala et al., 2018;
59 Esguerra et al., 2018; Cui et al, 2018; Lorente-Cebrián et al., 2019). Dysregulation of some
60 miRNAs and lncRNAs disrupts the gene regulatory network, leading to metabolic syndrome and
61 other related diseases. MiRNAs are ~22nt non-coding small RNAs that negatively regulate gene
62 expression at the post-transcriptional level (Bartel, 2004). Extensive research suggests that many
63 miRNAs, such as miR-9 (Hu el al., 2018), miR-20b-5p (Katayama el al., 2019; Gentile et al.,
64 2019), miR-802 (Kornfeld el al., 2013), let-7f (Gentile el al., 2019), miR-33 (Rayner el al.,
65 2010), miR-375 (Sedgeman el al., 2019), and others are involved in glucose homeostasis,
66 diabetes mellitus, abdominal obesity and cholesterol metabolism. Furthermore, some lncRNAs, a
67 novel class of long noncoding RNA larger than 200nt, have been reported to be involved in the
68 pathogenesis of type 2 diabetes mellitus and metabolic syndrome (Singer, Sussel, 2018; Losko,
69 Kotlinowski, Jura, 2016; Wang et al., 2018).
70   Due to the important effects of metabolic syndrome on human health, it is urgent to develop
71 database dedicated to various biomarkers associated with metabolic syndrome, such as genes,
72 miRNAs and lncRNAs. In recent years, several data resources and tools have been developed for
73 storing metabolic disease-associated biomolecules, such as T-HOD, metabolicMine,
74 PathCaseMAW, HMA and BioM2MetDisease. T-HOD (Dai et al., 2013) is a literature-based
75 candidate gene database currently containing 837, 835 and 821 candidate genes for hypertension,
76 obesity and diabetes, respectively. metabolicMine (Lyne et al., 2013) is a data warehouse with a
77 specific focus on the genomics, genetics and proteomics of common metabolic diseases.
78 PathCaseMAW (Cicek et al., 2013) provides a database-enabled framework and web-based
79 computational tools for browsing, querying, analyzing and visualizing stored metabolic

80   networks. HMA (Pornputtapong, Nookaew, Nielsen, 2015) is a human metabolic atlas website
81   providing information about human metabolism. These four software resources described above
82   provide important support for the study of the pathogenesis of metabolic diseases. However, they
83   do not contain non-coding RNA information related to metabolic diseases. BioM2MetDisease
84   (Xu et al., 2017) is a manually curated database containing 2681 entries of associations between
85   1147 biomolecules and 78 metabolic diseases. Though it is a very useful tool for studying
86   metabolic diseases, BioM2MetDisease is not a database dedicated to metabolic syndrome. It
87   contains miRNAs associated with 78 metabolic diseases but does not include hypertension and
88   hypo-HDL cholesterolemia, which are two important traits of metabolic syndrome. In addition, it
89   does not contain lncRNAs associated with metabolic syndrome and miRNAs from the last two
90   years.
91   In addition to the five data resources described above, there are other resources and tools for
92   studying human diseases. miR2Disease (Jiang et al., 2009) is a manually curated database which
93   contains 1939 curated relationships between 299 human miRNAs and 94 human diseases.
94   phenomiR (Ruepp, Kowarsch, Theis, 2012) provides miRNA and target relations from these
95   studies on the association of dysregulated miRNAs and diseases. HMDB (v3.0) (Wishart et al.,
96   2012) is a resource dedicated to the human metabolome, which includes more than 40,000
97   annotated metabolite entries. HMDD (v3.0) (Huang et al., 2018) manually collects a significant
98   number of miRNA-disease association entries. All these databases provide valuable tools for
99   exploring the roles of these biomolecules in human diseases, but they are not designed
100   specifically for metabolic syndrome. When faced with so many data resource options, it is
101   difficult to find the desired data for doctors who focus on metabolic syndrome. In addition, more
102   and more non-coding RNAs associated with metabolic syndrome have been discovered in the
103   last two years (Saeedi et al., 2019; Zhang et al., 2019; Zhang et al., 2018; Smieszek et al., 2019;
104   Lin et al., 2019).
105   So far, there is still no non-coding RNA database dedicated to metabolic syndrome. There is
106   an urgent need for a specialized data resource containing all the latest non-coding RNAs
107   associated with metabolic syndrome. To meet this demand, we have implemented the
108   ncRNA2MetS database which contains the latest and most complete MetS-miRNA (lncRNA)
109   association validated by various biological experiments. We carefully reviewed 571 articles
110   about relationship between various metabolic syndrome trait and non-coding RNA and gained
111   1068 associations between five metabolic syndrome traits and 627 non-coding RNAs (543
112   miRNAs and 84 lncRNAs) in four species. We hope that this database can help doctors
113   specializing in metabolic syndrome to explore the pathogenesis and treatments of metabolic
114   syndrome.
115
116   **Materials & Methods**

117   **Data collection from literature in PubMed**

118   According to the International Diabetes Federation (IDF) definition, a person with metabolic
119 syndrome must have central obesity (defined as waist circumference with ethnicity-specific
120 values) plus any two of the following four factors: (1) raised triglycerides, or specific treatment
121 for this lipid abnormality; (2) reduced HDL cholesterol, or specific treatment for this lipid
122 abnormality; (3) raised blood pressure, or treatment of previously diagnosed hypertension; (4)
123 raised fasting plasma glucose, or previously diagnosed type 2 diabetes (Alberti et al., 2005;
124 International Diabetes Federation, 2006). Therefore, we divided the risk factors of metabolic
125 syndrome into five traits: central obesity, type 2 diabetes mellitus, hypertension,
126 hypertriglyceridemia and hypo-HDL cholesterolemia.
127   Referring to Xu's method (Xu et al., 2017), we manually collected and curated MetS-miRNA
128 (lncRNA) association from related articles in the PubMed database. First, we used 'non-coding
129 RNA', 'ncRNA', 'microRNA', 'miRNA', 'long non-coding RNA', 'lncRNA' and each
130 metabolic syndrome trait as search terms to search the PubMed database by Title/Abstract
131 retrieval method. As a result, we gained more than 3000 related articles published since 2007.
132 We filtered out a large number of irrelevant articles or reviews by reading abstracts and finally
133 selected 571 articles that were really focused on association between metabolic syndrome trait
134 and miRNAs (lncRNA). Then, we manually extracted MetS-miRNA (lncRNA) association by
135 reading these selected articles in detail. In the process of extracting these associations, the
136 detailed information about MetS-miRNA (lncRNA) association were collected, including non-
137 coding RNA category, miRNA (lncRNA) name, name of metabolic syndrome trait, ICD-11
138 classification and DO (Disease Ontology) identifier for metabolic syndrome trait, method for
139 validation (e.g. RNA-seq, luciferase report assays, gene knock-out), detected tissue (e.g. serum,
140 adipose tissue, liver), expressive patterns (e.g. up-regulation, down-regulation, differential
141 expression), name of the gene regulated by miRNA (lncRNA), species involved (e.g. homo
142 sapiens, mus musculus, rattus norvegicus), referenced article (PubMed ID, title, year of
143 publication) and a brief introduction to this associations in the referenced article. Following
144 previous research rules (Jiang et al., 2009; Xu et al., 2017; Huang et al., 2018), we only collected
145 MetS-miRNA (lncRNA) association validated by various biological experiments in this process.
146 At the same time, in order to ensure the authenticity and reliability of the extracted information,
147 each MetS-miRNA (lncRNA) association was confirmed by at least two scholars. Finally, in
148 order to ensure consistency with other data resources, we standardized the names of miRNAs,
149 lncRNAs and metabolic syndrome traits. We provided miRBase (Kozomara, Birgaoanu,
150 Griffiths-Jones, 2019) identifier for miRNAs, NONCODE (Fang et al., 2017) identifier for
151 lncRNAs, ICD-11 classification and DO identifier for metabolic syndrome trait. The
152 construction process of the ncRNA2MetS database is shown in Figure 1.

153 **Database and website development**

154 In order to facilitate users to access and use the data in the ncRNA2MetS database, we developed
155 a user-friendly website providing data browsing, searching and downloading function. The
156 website was implemented in Java programing language, and all data were stored in MySQL
157 database. The website is freely available at http://www.biomed-bigdata.com:50020/index.html

158

Results

Database contents

161 By April 2019, we gained 3699 potential articles from PubMed using "Title/Abstract" searching.
162 After manual screening according to the relevance of the research content, 571 articles were
163 selected for reading in detail, and 1068 MetS-miRNA (lncRNA) associations were identified
164 finally. To describe MetS-miRNA (lncRNA) association in more detail, each record about MetS-
165 miRNA (lncRNA) association in ncRNA2MetS database consists of non-coding RNA category,
166 miRNA (lncRNA) name, miRBase identifier for miRNA, NONCODE identifier for lncRNA,
167 name of metabolic syndrome trait, ICD-11 classification and DO identifier for metabolic
168 syndrome trait, method for validation, detected tissue, expressive patterns, name of the gene
169 regulated by miRNA (lncRNA), species involved, information of cited articles and a brief
170 introduction to the associations in this referenced article. (see Materials and Methods). Currently,
171 the ncRNA2MetS database contains 1068 associations between five metabolic syndrome traits
172 (central obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia and hypo-HDL
173 cholesterolemia) and 627 non-coding RNAs (543 miRNAs and 84 lncRNAs) in four species
174 (homo sapiens, mus musculus, rattus norvegicus and Sus scrofa). Among the 1068 associations,
175 the number of miRNAs related to central obesity, type 2 diabetes mellitus, hypertension,
176 hyperlipidemia and hypo-HDL cholesterolemia are 288, 207, 96, 50 and 41, respectively. In
177 addition, the number of miRNAs reported to be related to metabolic syndrome is 36 (Figure 2a).
178 The number of lncRNAs related to central obesity, type 2 diabetes mellitus, hypertension,
179 hyperlipidemia, hypo-HDL cholesterolemia and metabolic syndrome are 42, 28, 12, 1, 2 and 3,
180 respectively (Figure 2b).

Database interface

182 ncRNA2MetS database implements a user-friendly website interface through which users can
183 access all data in ncRNA2MetS conveniently and easily. The website consists of six parts,
184 namely HOME, BROWSE, SEARCH, DOWNLOAD, SUBMIT and HELP. The 'HOME' page
185 shows a brief introduction about metabolic syndrome, miRNA and lncRNA while 'BROWSE'
186 page (Figure 3a) and 'SEARCH' page (Figure 3b) provide data query. On the 'BROWSE' page,
187 users can click a specific miRNA, lncRNA or metabolic syndrome trait to browse the MetS-
188 ncRNA associations. Then, the website will return all MetS-ncRNA associations that meet the
189 query criteria. If too many association entries are returned, users can specify ncRNA category,
190 species or validation methods to screen for required entries. For example, if users specify 'homo
191 sapiens' as species, the website will return all associations related to 'homo sapiens' (Figure 3c).
192 The 'SEARCH' page provides users with faster and more accurate query method, which
193 support 'Accurate Search' and 'Fuzzy Search'. For 'Accurate Search', users can input an
194 accurate miRNA (lncRNA) name or metabolic syndrome trait name, or both, then click 'Search'
195 button to query the required associations. On the contrary, for 'Fuzzy Search', users only need to
196 input partial names of a miRNA (lncRNA) or metabolic syndrome trait to query the required

197 relationships. It should be noted that query keywords are case-insensitive. In addition, users can
198 specify 'Validated Methods' to narrow query scope. For example, if the user specifies 'qRT-
199 PCR' as the validated method, the website will return all associations that match query keywords
200 and have been validated by qRT-PCT. Similar to 'BROWSE', in the search result page, users can
201 also filter MetS-ncRNA association by selecting specified ncRNA category, species or validated
202 method. Finally, users can browse the detailed information about a specific MetS-ncRNA
203 association by clicking a hyperlink to the 'Details' page (Figure 3d).
204   In addition to freely querying MetS-ncRNA association stored in ncRNA2MetS, users can
205 also submit novelty associations validated by their own experiments. They can do this on the
206 'SUBMIT' page (Figure 3e) and must provide detailed information about the new association.
207 Our committee will regularly review new submissions. Once the submitted association is
208 confirmed, it will be added into ncRNA2MetS. Furthermore, users can freely and easily
209 download all MetS-ncRNA associations in the 'DOWNLOAD' page. Finally, if users encounter
210 any difficulties or problems in using the ncRNA2MetS, they can find help information on
211 'HELP' page or contact us via e-mail.

212 **Examples of using ncRNA2MetS**

213 In this section, we will use examples to show you how to use the ncRNA2MetS database. First,
214 users can input 'miR-155-5p' as the miRNA name on the 'SEARCH' page and then click the
215 'Search' button. A result page will be returned and will display all records about miR-155-5p,
216 including those of different species and various metabolic syndrome traits. On the result page,
217 one can easily notice that miR-155-5p is related to all five metabolic syndrome traits, which
218 implies that it has a very important impact on metabolic syndrome. In fact, miR-155-5p has been
219 reported to be a risk factor of metabolic syndrome. ncRNA2MetS also supports searching by the
220 name of metabolic syndrome trait, and this can facilitate the study of pathogenesis for a certain
221 specific metabolic syndrome trait. For example, users can input 'obesity' as the name of
222 metabolic syndrome trait on the 'SEARCH' page and will find that a number of miRNAs and
223 lncRNAs such as miR-21, miR-155-5p and Paral1 showed abnormal expression in human
224 obesity. The introduction to these associations in ncRNA2MetS shows that a reduced level of
225 miR-21 might be associated with obesity and its related metabolic traits such as
226 hyperinsulinemia (Ghorbani et al., 2018); Obese subjects have increased expressions of miR-
227 155-5p and miR-122, two miRNAs related to inflammation and iron metabolism, respectively, at
228 both the systemic and sperm levels (López et al., 2018); Furthermore, a novel component of the
229 adipogenic transcriptional regulatory network defining the lncRNA Paral1 is identified as an
230 obesity-sensitive regulator of adipocyte differentiation and function (Firmin, et al., 2017).
231   As a feature, ncRNA2MetS also supports querying lncRNAs associated with metabolic
232 syndrome. For example, by inputting 'H19', the result page will show all records of relations
233 between 'H19' and various metabolic syndrome traits including obesity, type 2 diabetes mellitus
234 and hypo-HDL cholesterolemia in three species. The functional description in ncRNA2MetS
235 shows that imprinted lncRNA H19 increases upon cold-activation and decreases in obesity in
236 BAT (Schmidt et al., 2018); Related studies reveal a previously undescribed double-negative

237   feedback loop between sponge lncRNA and target miRNA that contributes to glucose regulation
238   in muscle cells (Gao et al., 2014); A H19-miR130b pathway regulating lipid metabolism and
239   inflammation response in ox-LDL-treated Raw264.7 cells provides new targets for
240   atherosclerosis treatment (Han et al., 2018). Overall, ncRNA2MetS can be used as a high-
241   quality and most complete data resource for studying the roles of miRNAs and lncRNAs
242   involved in metabolic syndrome.

243   **Database analysis**

244   Currently, ncRNA2MetS provides almost all the research results related to the association
245   between metabolic syndrome and non-coding RNA. Comprehensive analysis of the data in
246   ncRNA2MetS can help people better explore the relationship between metabolic syndrome and
247   non-coding RNA. For this purpose, a relational network between metabolic syndrome traits and
248   ncRNAs (miRNAs and lncRNAs) is constructed using Cytoscape software (Figure 4). In the
249   MetS-ncRNA association network, nodes represent metabolic syndrome traits and ncRNA, and
250   edges represent the relationships between them. For miRNAs and lncRNAs, degree represents
251   the number of associated metabolic syndrome traits, and also indicates their importance for
252   researching the pathogenesis and treatment of metabolic syndrome. Fig. 4 shows that the degrees
253   of miR-122, miR-155-5p and miR-146a-5p (green node) were largest among the numerous
254   miRNAs, which are related to all five metabolic syndrome traits (obesity, type 2 diabetes
255   mellitus, hypertension, hyperlipidemia and hypo-HDL cholesterolemia), or have been reportedly
256   involved in metabolic syndrome. This result implies that these three miRNAs plays an important
257   role in the study of metabolic syndrome. In addition, the lncRNA with the highest degree is H19,
258   which is related to obesity, type 2 diabetes mellitus, and hypo-HDL cholesterolemia, and is
259   reported to be involved in the pathogenesis of metabolic syndrome. Further and deeper analysis
260   of the ncRNA2MetS data will yield more interesting results.

261

262   # Discussion
263   Metabolic syndrome has become one of the most important diseases threatening human health
264   worldwide. There is increasing evidence suggesting that metabolic syndrome is associated with
265   abnormal expression of some ncRNAs, including miRNA and lncRNAs. A database dedicated to
266   metabolic syndrome-non-coding RNA association is helpful in studying the pathogenesis and
267   treatments of metabolic syndrome. For this purpose, we developed ncRNA2MetS, a database
268   containing almost all experimentally supported metabolic syndrome-non-coding RNA
269   associations. Currently, ncRNA2MetS contains 1068 validated associations between five
270   metabolic syndrome traits and 627 ncRNAs (543 miRNAs and 84 lncRNAs) in four species.
271   In recent years, some researchers have developed several high-quality databases, such as
272   BioM2MetDisease (Xu et al., 2017) and HMDD (Huang et al., 2018), to provide metabolic
273   disease-miRNAs associations. Nevertheless, these databases are not dedicated to metabolic
274   syndrome and do not cover all the metabolic syndrome traits. For example, BioM2MetDisease
275   contains 2681 entries of relationships between 524 miRNAs and 45 metabolic diseases across 14

276   species. This is a database with very rich storage content, but it is not specifically for metabolic
277   syndrome. Though BioM2MetDisease contains a large number of miRNAs associated with
278   obesity, type 2 diabetes mellitus and dyslipidemia, it lacks miRNA information related to
279   hypertension and hypo-HDL cholesterolemia. Furthermore, although a large number of new
280   miRNAs and lncRNAs related to metabolic syndrome have been identified and reported in the
281   past two years, BioM2MetDisease has not been updated with the latest findings. HMDD (v3.0) is
282   a database that curates experiment-supported evidence for human miRNA and disease
283   associations. Currently, HMDD contains 32281 miRNA-disease association entries which
284   include 1102 miRNA genes and 850 diseases. Similar to BioM2MetDisease, HMDD is not
285   specifically for metabolic syndrome, and it does not contain miRNAs associated with hypo-HDL
286   cholesterolemia. Furthermore, the number of miRNAs contained in HMDD is far less than
287   ncRNA2MetS. To demonstrate the value of ncRNA2MetS, we comprehensively compared the
288   amount of non-coding RNAs associated with various metabolic syndrome traits contained in
289   BioM2MetDisease, HMDD and ncRNA2MetS. The results showed that ncRNA2MetS contains
290   significantly more miRNAs associated with metabolic syndrome than both BioM2MetDisease
291   and HMDD (Figure 5a). More concretely, the number of miRNAs associated with obesity, type 2
292   diabetes mellitus, hypertension, hypertriglyceridemia, hypo-HDL cholesterolemia and metabolic
293   syndrome were 225, 204, 0, 24, 0 and 39 in BioM2MetDisease; 80, 128, 65, 8, 0 and 38 in
294   HMDD; and 288, 207, 96, 50, 41 and 36 in ncRNA2MetS, respectively. Finally, ncRNA2MetS
295   provides not only miRNAs but also lncRNAs associated with metabolic syndrome, and covers
296   the latest research findings up to April 2019.
297   The prevalence of metabolic syndrome, including central obesity, type 2 diabetes mellitus,
298   hypertension, hypertriglyceridemia and hypo-HDL cholesterolemia, is growing globally, and the
299   amount of studies on metabolic syndrome is also increasing rapidly. To illustrate the research
300   trend of ncRNAs related to metabolic syndrome, we counted the number of articles about non-
301   coding RNA studies related to metabolic syndrome between 2007 and April 2019 (Figure 5b).
302   Clearly, the amount of research about the association between ncRNAs and metabolic syndrome
303   has increased rapidly in the past two years. Therefore, it will become a trend that more and more
304   metabolic syndrome-non-coding RNA associations will be identified and validated in the future.
305   We will keep track of the latest advances in the study of relationship between metabolic
306   syndrome and non-coding RNA, and update ncRNA2MetS database regularly. In addition, we
307   will focus on more types of non-coding RNA such as circular RNA, snoRNA, etc. and add
308   associations between metabolic syndrome and these ncRNAs into ncRNA2MetS to increase its
309   coverage. Furthermore, we will develop more powerful data analysis tools such as network
310   visualization tool to help researchers better study the pathogenesis and treatment of metabolic
311   syndrome in the future. In a word, we hope that ncRNA2MetS can be used as an effective tool
312   for studying the mechanism of non-coding RNA in metabolic syndrome.
313
314   **Conclusions**

315 A growing number of studies have suggested that many non-coding RNAs, including miRNAs
316 and lncRNA, are involved in metabolic syndrome and its traits. In this article, we introduced
317 ncRNA2MetS, a user-friendly web-based tool developed for curating the association between
318 metabolic syndrome and ncRNAs (miRNA and lncRNAs). ncRNA2MetS currently contains
319 1068 associations between five metabolic syndrome traits and 627 ncRNAs (543 miRNAs and
320 84 lncRNAs) in four species. ncRNA2MetS has covered almost all relevant research about the
321 association between metabolic syndrome and ncRNAs between 2007 and 2019. It is expected
322 that ncRNA2MetS will serve as a valuable data resource that will help researchers better study
323 the pathogenesis and treatments of metabolic syndrome.
324

325 **References**
326 **Alberti KGMM, Zimmet P, Shaw J. 2005.** The metabolic syndrome--a new worldwide
327 definition. *The Lancet* 366(9491):1059-1062 DOI 10.1016/S0140-6736(05)67402-8
328 **Bartel DP. 2004.** MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 116(2):
329 281-297 DOI 10.1016/S0092-8674(04)00045-5.
330 **Cicek A E, Qi XJ, Cakmak A, Johnson SR, Han X, Alshalwi S, Ozsoyoglu ZM, Ozsoyoglu**
331 **G. 2013.** An online system for metabolic network analysis. *Database: The Journal of Biological*
332 *Databases and Curation* 2014 DOI 10.1093/database/bau091.
333 **Cui XW, Tan JM, Shi YJ, Sun C, Li Y, Ji CB, Wu J, Zhang Z, Chen SY, Guo XR, Liu C.**
334 **2018.** The long non-coding RNA Gm10768 activates hepatic gluconeogenesis by sequestering
335 microRNA-214 in mice. *The Journal of Biological Chemistry* 293(11): 4097-4109 DOI
336 10.1074/jbc.M117.812818.
337 **Dai HJ, Wu JCY, Tsai RTH, Pan WH, Hsu WL. 2013.** T-HOD: a literature-based candidate
338 gene database for hypertension, obesity and diabetes. *Database: The Journal of Biological*
339 *Databases and Curation* 2013 DOI 10.1093/database/bas061.
340 **Esguerra JLS, Nagao M, Ofori JK, Wendt A, Eliasson L. 2018.** MicroRNAs in islet hormone
341 secretion. *Diabetes, Obesity and Metabolism* 20(S2): 11-19 DOI 10.1111/dom.13382.
342 **Fang SS, Zhang LL, Guo JC, Niu YW, Wu Y, Li H, Zhao LH, Li XY, Teng XY, Sun XH,**
343 **Sun L, Zhang MQ, Chen RS, Zhao Y. 2017.** NONCODE V5: a comprehensive annotation
344 database for long non-coding RNAs. *Nucleic Acids Research* 46(D1): D308-D314 DOI
345 10.1093/nar/gkx1107.
346 **Firmin FF, Oger F, Gheeraert C, Dubois-Chevalier J, Vercoutter-Edouart AS, Alzaid F,**
347 **Mazuy C, Dehondt H, Alexandre J, Derudas B, Dhalluin Q, Ploton M, Berthier A,**
348 **Woitrain E, Lefebvre T, Venteclef N, Pattou F, Staels B, Eeckhoute J, Lefebvre P. 2017.**
349 The RBM14/CoAA-interacting, long intergenic non-coding RNA Paral1 regulates adipogenesis
350 and coactivates the nuclear receptor PPARγ. *Scientific Reports* 7(1): 14087 DOI
351 10.1038/s41598-017-14570-y.
352 **Gao Y, Wu FJ, Zhou JC, Yan L, Jurczak MJ, Lee HY, Yang LH, Mueller M, Zhou XB,**
353 **Dandolo L, Szendroedi LJ, Roden M, Flannery C, Taylor H, Carmichael GG, Shulman GI,**
354 **Huang YQ. 2014.** The H19/let-7 double-negative feedback loop contributes to glucose

355   metabolism in muscle cells. *Nucleic Acids Research* 42(22): 13799-13811 DOI
356   10.1093/nar/gku1160.
357   **Gentile AM, Lhamyani S, Coín-Aragüez L, Clemente-Postigo M, Olivera WO, Romero-**
358   **Zerbo SY, García-Serrano S, García-Escobar E, Zayed H, Doblado E, Bermúdez-Silva FJ,**
359   **Murri M, Tinahones FJ, Bekay RE. 2019.** miR‐20b, miR‐296, and Let‐7f Expression in
360   Human Adipose Tissue is Related to Obesity and Type 2 Diabetes. *Obesity* 27(2): 245-254 DOI
361   10.1002/oby.22363.
362   **Ghorbani S, Mahdavi R, Alipoor B, Panahi G, Esfahani EN, Razi F, Taghikhani M,**
363   **Meshkani R. 2018.** Decreased serum microRNA-21 level is associated with obesity in healthy
364   and type 2 diabetic subjects. *Archives of Physiology Biochemistry* 124(4): 300-305 DOI
365   10.1080/13813455.2017.1396349.
366   **Han Y, Ma J, Wang JP, Wang LP. 2018.** Silencing of H19 inhibits the adipogenesis and
367   inflammation response in ox-LDL-treated Raw264. 7 cells by up-regulating miR-130b.
368   *Molecular Immunology* 93: 107-114 DOI 10.1016/j.molimm.2017.11.017.
369   **Hu DZ, Wang Y, Zhang HY, Kong DL. 2018.** Identification of miR-9 as a negative factor of
370   insulin secretion from beta cells. *Journal of Physiology and Biochemistry* 74(2): 291-299 DOI
371   10.1007/s13105-018-0615-3.
372   **Huang Z, Shi JC, Gao YX, Cui CM, Zhang S, Li JW, Zhou Y, Cui QH. 2018.** HMDD v3. 0:
373   a database for experimentally supported human microRNA–disease associations. *Nucleic Acids*
374   *Research* 47(D1): D1013-D1017 DOI 10.1093/nar/gky1010.
375   **International Diabetes Federation. 2006.** The IDF consensus worldwide definition of the
376   metabolic syndrome. *Brussels: International Diabetes Federation.* 2006: 4
377   **Jiang QH, Wang YD, Hao YY, Juan LR, Teng MX, Zhang XJ, Li MM, Wang GH, Liu YL.**
378   **2009.** miR2Disease: a manually curated database for microRNA deregulation in human disease.
379   *Nucleic Acids Research* 37(suppl_1): D98-D104 DOI 10.1093/nar/gkn714.
380   **Katayama M, Wiklander OPB, Fritz T, Caidahl K, EI-Andaloussi S, Zierath JR, Krook A.**
381   **2019.** Circulating Exosomal miR-20b-5p Is Elevated in Type 2 Diabetes and Could Impair
382   Insulin Action in Human Skeletal Muscle. *Diabetes* 68(3): 515-526 DOI 10.2337/db18-0470.
383   **Kornfeld JW, Baitzel C, Könner AC, Nicholls HT, Vogt MC, Herrmanns K, Scheja L,**
384   **Haumaitre C, Wolf AM, Knippschild U, Seibler J, Cereghini S, Heeren J, Stoffel M,**
385   **Brüning JC. 2013.** Obesity-induced overexpression of miR-802 impairs glucose metabolism
386   through silencing of Hnf1b. *Nature* 494: 111-115 DOI 10.1038/nature11793.
387   **Kozomara A, Birgaoanu M, Griffiths-Jones S. 2019.** miRBase: from microRNA sequences to
388   function. *Nucleic Acids Research* 47(D1): D155-D162 DOI 10.1093/nar/gky1141.
389   **La Sala L, Micheloni S, De Nigris V, Prattichizzo F, Ceriello A. 2018.** Novel insights into the
390   regulation of miRNA transcriptional control: implications for T2D and related complications.
391   *Acta Diabetologica* 55(10): 989-998 DOI 10.1007/s00592-018-1149-4.
392   **López P, Castro A, Flórez M, Miranda K, Aranda P, Sánchez-González C, Llopis J,**
393   **Arredondo M. 2018.** miR-155 and miR-122 expression of spermatozoa in obese subjects.
394   *Frontiers in Genetics* 9: 175 DOI 10.3389/fgene.2018.00175.

395 **Lorente-Cebrián S, González-Muniesa P, Milagro FI, Martínez JA. 2019.** MicroRNAs and
396 other non-coding RNAs in adipose tissue and obesity: emerging roles as biomarkers and
397 therapeutic targets. *Clinical Science* 133(1): 23-40 DOI 10.1042/CS20180890.
398 **Losko M, Kotlinowski J, Jura J. 2016.** Long noncoding RNAs in metabolic syndrome related
399 disorders. *Mediators of Inflammation* 2016: 1-12 DOI 10.1155/2016/5365209c.
400 **Lyne M, Smith RN, Lyne R, Aleksic J, Hu FY, Kalderimis A, Stepan R, Micklem G. 2013.**
401 metabolicMine: an integrated genomics, genetics and proteomics data warehouse for common
402 metabolic disease research. *Database: The Journal of Biological Databases and Curation* 2013
403 DOI 10.1093/database/bat060.
404 **Pornputtapong N, Nookaew I, Nielsen J. 2015.** Human metabolic atlas: an online resource for
405 human metabolism. *Database: The Journal of Biological Databases and Curation* 2015 DOI
406 10.1093/database/bav068.
407 **Rayner KJ, Suárez Y, Dávalos A, Parathath S, Fitzgerald ML, Tamehiro N, Fisher EA,**
408 **Moore KJ, Fernández-Hernando C. 2010.** MiR-33 contributes to the regulation of cholesterol
409 homeostasis. *Science* 328(5985): 1570-1573 DOI 10.1126/science.1189862.
410 **Ruepp A, Kowarsch A, Theis F. 2012.** PhenomiR: MicroRNAs in human diseases and
411 biological processes. *Next-Generation MicroRNA Expression Profiling Technology*. Humana
412 Press, 2012: 249-260 DOI 10.1007/978-1-61779-427-8_17.
413 **Saeedi Borujeni MJ, Esfandiary E, Baradaran A, Valiani A, Ghanadian M, Codoñer-**
414 **Franch P, Basirat R, Alonso-Iglesias E, Mirzaei H, Yazdani A. 2019.** Molecular aspects of
415 pancreatic β -cell dysfunction: Oxidative stress, microRNA, and long noncoding RNA. *Journal*
416 *of Cellular Physiology* 234(6): 8411-8425 DOI 10.1002/jcp.27755.
417 **Schmidt E, Dhaouadi I, Gaziano I, Oliverio M, Klemm P, Awazawa M, Mitterer G,**
418 **Fernandez-Rebollo E, Pradas-Juni M, Wagner W, Hammerschmidt P, Loureiro R, Kiefer**
419 **C, Hansmeier NR, Khani S, Bergami M, Heine M, Ntini E, Frommolt P, Zentis P, Ørom**
420 **UA, Heeren J, Blüher M, Bilban M, Kornfeld JW. 2018.** LincRNA H19 protects from dietary
421 obesity by constraining expression of monoallelic genes in brown fat. *Nature Communications.*
422 9(1): 3622 DOI 10.1038/s41467-018-05933-8.
423 **Sedgeman LR, Beysen C, Solano MAR, Michell DL, Sheng QH, Zhao SL, Turner S, Linton**
424 **MF, Vickers KC. 2019.** Beta cell secretion of miR-375 to HDL is inversely associated with
425 insulin secretion. *Scientific Reports* 9(1): 3803 DOI 10.1038/s41598-019-40338-7.
426 **Singer RA, Sussel L. 2018.** Islet long noncoding RNAs: a playbook for discovery and
427 characterization. *Diabetes* 67(8): 1461-1470 DOI 10.2337/dbi18-0001.
428 **Smieszek A, Kornicka K, Szłapka-Kosarzewska J, Androvic P, Valihrach L, Langerova L,**
429 **Rohlova E, Kubista M, Marycz K. 2019.** Metformin Increases Proliferative Activity and
430 Viability of Multipotent Stromal Stem Cells Isolated from Adipose Tissue Derived from Horses
431 with Equine Metabolic Syndrome. *Cells* 8(2): 80 DOI 10.3390/cells8020080.
432 **Stoll L, Sobel J, Rodriguez-Trejo A, Guay C, Lee KL, Venø MT, Kjems J, Laybutt DR,**
433 **Regazzi R. 2018.** Circular RNAs as novel regulators of β-cell functions in normal and disease
434 conditions. *Molecular Metabolism* 9: 69-83 DOI 10.1016/j.molmet.2018.01.010.

435 **Wang JP, Yang WL, Chen ZZ, Chen J, Meng YH, Feng BQ, Sun LB, Dou L, Li J, Cui QH,**
436 **Yang JC. 2018.** Long noncoding RNA lncSHGL recruits hnRNPA1 to suppress hepatic
437 gluconeogenesis and lipogenesis. *Diabetes* 67(4): 581-593 DOI 10.2337/db17-0799.
438 **Wishart DS, Jewison T, Guo AC, Wilson M, Knox C, Liu YF, Djoumbou Y, Mandal R,**
439 **Aziat F, Dong E, Bouatra S, Sinelnikov I, Arndt D, Xia JG, Liu P, Yallou F, Bjorndahl T,**
440 **Perez-Pineiro R, Eisner R, Allen F, Neveu V, Greiner R, Scalbert A. 2013.** HMDB 3.0—the
441 human metabolome database in 2013. *Nucleic Acids Research* 41(D1): D801-D807 DOI
442 10.1093/nar/gks1065.
443 **Li XH, Tang SJ, Gui WW, Erik M, Tao TT, Li L, Wu F, Zhou JQ, Zheng FP, Li H. 2019.**
444 Circulating miR-143-3p inhibition protects against insulin resistance in Metabolic Syndrome via
445 targeting of the insulin-like growth factor 2 receptor. *Translational Research* 205: 33-43 DOI
446 10.1016/j.trsl.2018.09.006.
447 **Xu YJ, Yang HX, Wu T, Dong Q, Sun ZG, Shang DS, Li F, Xu YQ, Su F, Liu SY, Zhang**
448 **YP, Li X. 2017.** BioM2MetDisease: a manually curated database for associations between
449 microRNAs, metabolites, small molecules and metabolic diseases. *Database: The Journal of*
450 *Biological Databases and Curation* 2017 DOI 10.1093/database/bax037.
451 **Zhang BH, Shen CA, Zhu BW, An HY, Zheng B, Xu SB, Sun JC, Sun PC, Zhang W, Wang**
452 **J, Liu JY, Fan YQ. 2019.** Insight into miRNAs related with glucometabolic disorder.
453 *Biomedicine & Pharmacotherapy* 111: 657-665 DOI 10.1016/j.biopha.2018.12.123.
454 **Zhang X, Li DY, Reilly MP. 2019.** Long intergenic noncoding RNAs in cardiovascular
455 diseases: Challenges and strategies for physiological studies and translation. *Atherosclerosis* 281:
456 180-188 DOI 10.1016/j.atherosclerosis.2018.09.040.

Figure 1

The flowchart of the ncRNA2MetS database design
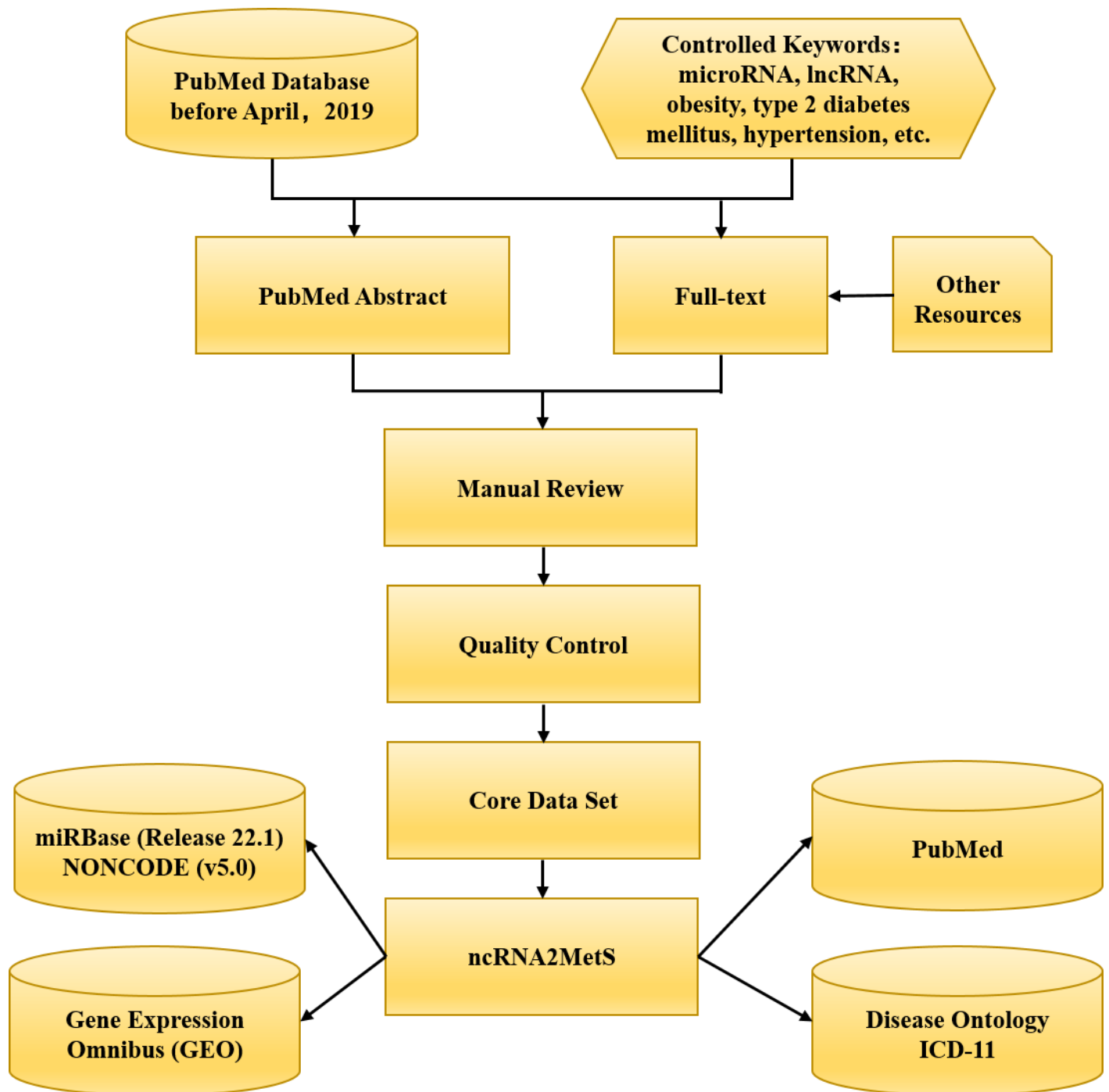
Figure 2

The statistics of non-coding RNAs contained in the ncRNA2MetS database

(A) The distribution of miRNAs in various metabolic syndrome traits. (B) The distribution of lncRNAs in various metabolic syndrome traits. (C) The distribution of miRNAs in different species. (D) The distribution of lncRNAs in different species.
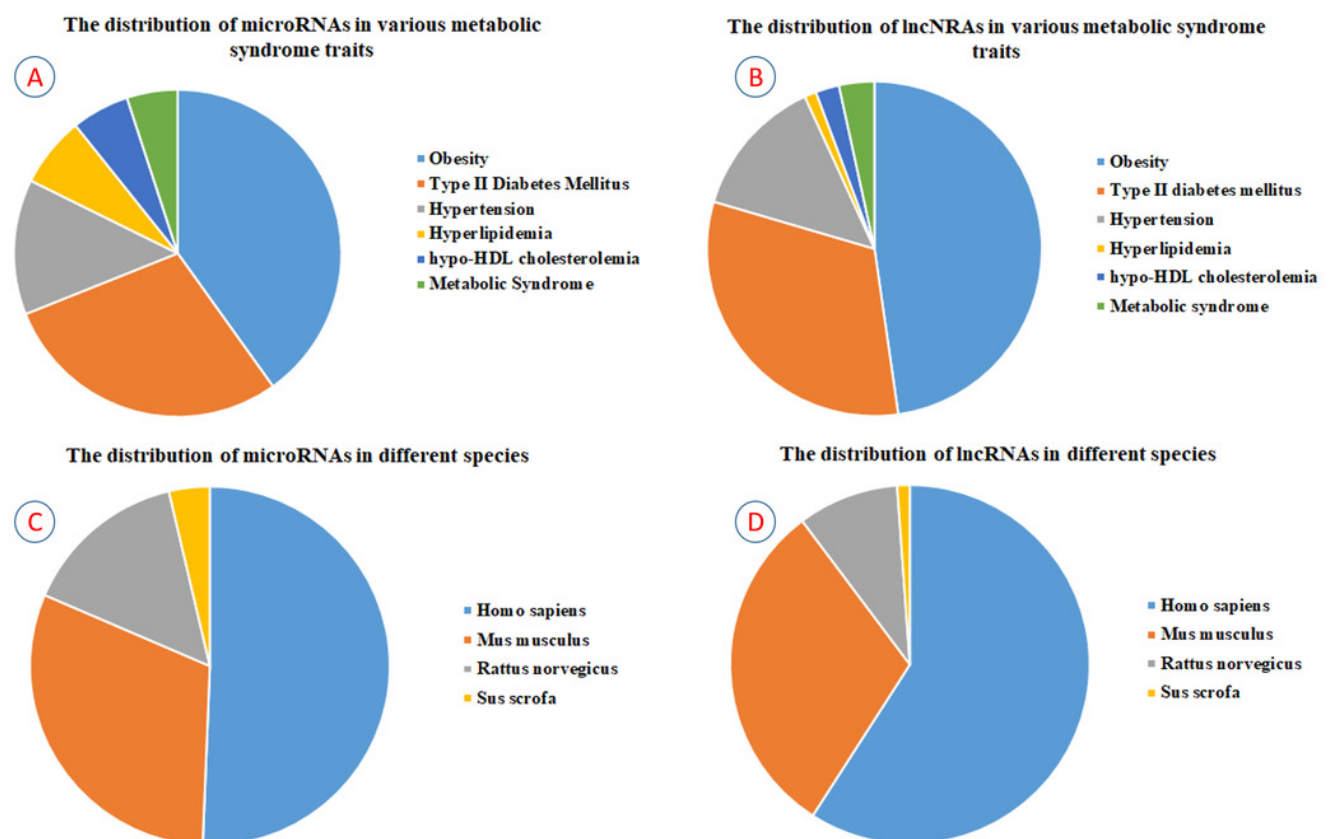
Figure 3

The schematic workflow of the ncRNA2MetS database

(A) Browse the data. (B) Search the data. (C) Browse the query results. (D) Browse the detail information about a specific MetS-ncRNA association. (E) Submit a new MetS-ncRNA association to the ncRNA2MetS database.

Figure 4

The MetS-ncRNA association network

Nodes correspond to non-coding RNAs (miRNAs and lncRNAs) and metabolic syndrome traits (central obesity, type 2 diabetes mellitus, hypertension, hyperlipidaemia and hypo-HDL cholesterolemia) and the edges correspond to experimentally supported associations. The size of the nodes corresponds to the nodes' degree.
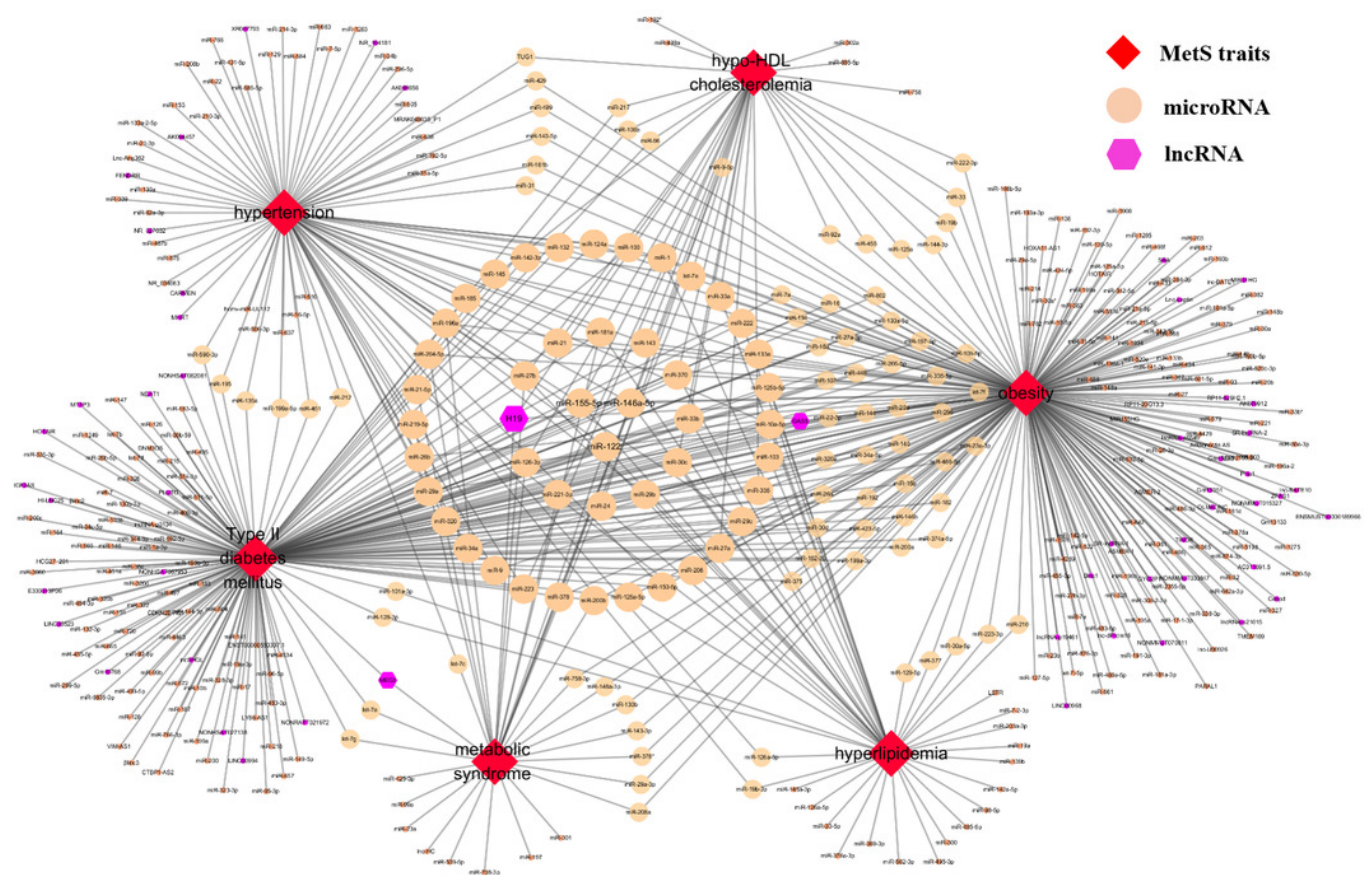
Figure 5

Comparison of the number of non-coding RNA in different databases

(A) Comparison of the number of non-coding RNAs associated with metabolic syndrome among BioM2MetDisease, HMDD and ncRNA2MetS. (B) Number of papers about non-coding RNAs associated with metabolic syndrome between 2007 and April 2019.