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## DbDMAD: a Database of DNA Methylation in Human Age-related Disease

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### Abstract

DNA methylation plays a variety of crucial roles in cell division, proliferation, development of aging life, development of genetic diseases related to uniparental disomy, and carcinogenesis. DNA methylation can be probed by HPLC and gene chip which is very helpful to the high-through methylation test. In recent years many published articles reported that DNA methylation may be linked with human aged disease. Mining and integration of DNA methylation in human aged disease can be beneficial to novel biological discoveries. There has not been DNA methylation database repository which is exclusive for human aged disease. Therefore, we developed dbDMAD: a database of DNA methylation in human aged diseases, there are two purposes of it, one is to store DNA methylation in human aged disease datasets which were obtained from laboratory experiments, another is to find the relationship of different aged diseases. This is the first release of dbDMAD in which users can find 12 kinds of human aged diseases and relevant DNA methylation information. It can be searched by disease name and gene ID. This database also includes a visualization tool named ChainMap, by which the map of methylation pathway can be shown.

**Index Terms:** dbDMAD; DNA Methylation; Aged Disease; Database

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### 1. Introduction

DNA methylation refers to the addition of a methyl (CH<sub>3</sub>) group to a DNA molecule [1]. In human somatic cells, DNA methylation preferentially involves the 5' cytosine in CpG dinucleotides [2]. The mediation of DNA methylation is a family of DNA methyltransferases which includes Dnmt1, Dnmt3a and Dnmt3b. Dnmt1 is maintenance Mtase which primarily replicates methylation patterns, while Dnmt3a and Dnmt3b are capable

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of methylating previously unmethylated DNA, referred to as de novo methylation [3]. DNA methylation has important roles in differentiation, X chromosome inactivation, genomic imprinting, maintenance of chromatin structure, and suppression of “parasitic” DNA [4]. Nowadays, a lot of analysis techniques to probe DNA methylation in human cell samples, such as HPLC, Methylation-specific PCR, and Methylation-specific gene chip. Different techniques provide information on DNA methylation at different levels, spanning from genome-wide methylation content to methylation of single residues in specific genes [5]. DNA methylation has two types: hypermethylation and hypomethylation. Both of them are occurring with aging. If DNA methylation level is lower than the normal level, which will be considered as hypomethylation. During the early molecular abnormalities, hypomethylation is one of the potential detections of cancer biomarkers [6]. Moreover, Hypermethylation of 5'-CpG islands of cancer suppressor genes can silence the gene and serve as an alternate to mutations [7]. So the most immediately potential usage of CpG hypermethylation will be as cancer biomarkers [8].

It has been found that DNA methylation was not only related with cancer, but also related with human aged diseases, such as arteriosclerosis, hypertension, etc. For this reason, we developed dbDMAD. The first use of it is to store DNA methylation, but it especially focuses on the data which owns information of the relationship between DNA methylation and human aged disease. It will be of great help both in the study of the DNA methylation and the roles of this modification in human aged disease. To establish this database, we manually curated 560 public articles in PubMed which had DNA methylation in 12 kinds of human aged disease information and created it named ‘dbDMAD’. Two search options were provided for advanced searches, namely disease name and gene ID. Furthermore, dbDMAD provides a visualization tool: ChainMap. When you click ChainMap, you can see the pathogenic pathway vividly. This tool can help users to find the connections of different human aged diseases.

## 2. Data Source

Firstly, we first searched PubMed by keywords such as ‘DNA methylation and heart disease’, ‘DNA methylation and diabetes’ and so on. Then we downloaded the search results that had been recorded before April 2010 from the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). From this search, we obtained about 560 papers which contained those keywords. Next we curated the data manually. The database includes hyperlinks to the original PubMed articles, and researchers who are interested in the article can get the details through the link.

At last, dbDMAD includes 432 gene’s information. According to the relationship between disease and gene or environment factor, for each article we draw chain map to help the users to see the pathway about human aged disease vividly.

Not only do we use our manual data source, but also use the public methylation data of human which formed into a public database—MethDB( <http://www.methdb.de> ). We extracted about 19081 data form MethDB, and these data were about human tumor. The data from MethDB had more detailed information about the DNA sequence and experiment results. We can use these data to design a model which can predict the methylation state of DNA.

## 3. Database Utility

dbDMAD provides two types of searching models on its search page (Fig.1A). One is the disease name search, another is gene ID search. Users can select one disease name or gene ID to browse page. Search and browse results list basic information (Fig.1B), such as related disease, gene ID, methylation style (hypermethylation or hypomethylation) and the original article name. More detailed information for each disease can be accessed by clicking the detailed link, as shown in fig. 1C. Detailed information contains the pathogenic site, the inducing factor, the pathogenic result and the sample of laboratory experiments, etc. For

example, users can enter the database first page 'search by disease name', then choose the arteriosclerosis in the search box, and then proceed. The result page will show 12 results about this disease. Each result will be listed in one row. As the first row shows, the related gene is P21<sup>ras</sup>, methylation style is hypomethylation. If click the detail column, it will enter the detail page, from this page, users can find that the pathogenic site is vascular endothelial cells, the inducing factor's homocysteine, the pathogenic result is vascular endothelial cells damage, and the sample of laboratory experiment is human umbilical vein endothelial cells and human aortic endothelial cells. Users also can know the methylation sites are P21<sup>ras</sup> C17, C18, C20, and C37(C means the methylated cytosine). dbDMAD also includes a visualization tool named ChainMap, by which methylation pathway will be shown vividly. We also give the same example as above shows. Fig. 1D is the map of the pathway.

**dbDMAD: a database of DNA methylation in human aged disease**

[Homepage](#) [Database](#) [Software](#) [Publications](#) [Documents](#)

**Search by Disease Name**

Please Select A Validated Disease Name ▼

**Query examples :** [Select the Disease Symbol](#)

**Search by Target Gene**


Please Select A Validated Gene Name ▼

**Query examples :** [Select the Gene Symbol](#)

**dbDMAD: a database of DNA methylation in human aged disease**

[Homepage](#) [Database](#) [Software](#) [Publications](#) [Documents](#) [People](#)

Disease Name	Gene Name	Article Name	Methylation Style	Year	Detail
arteriosclerosis	P21ras	Inhibition of growth and p21ras methylation in vascular endothelial cells by homocysteine but not cy	hypomethylation	1997	<a href="#">More..</a>
arteriosclerosis	EC-SOD	Local hypomethylation in atherosclerosis found in rabbit ec-sod gene	hypomethylation	1999	<a href="#">More..</a>
arteriosclerosis	global DNA	Mitogen-induced P53 downregulation precedes vascular smooth muscle cell migration from health tunic	hypomethylation	2001	<a href="#">More..</a>
arteriosclerosis	MTHFR	A common mutation in the 5,10-methylenetera-hydrofolate reductase gene affects genomic DNA methylati	hypomethylation	2001	<a href="#">More..</a>
arteriosclerosis	global DNA	DNA methylation smooth muscle cells and atherogenesis	hypomethylation	2003	<a href="#">More..</a>
arteriosclerosis	APOE	DNA methylation polymorphisms Precede Any histological sign of atherosclerosis in mice lacking apoli	hypomethylation	2004	<a href="#">More..</a>
arteriosclerosis	global DNA	The impact of metabolism on DNA methylation	hypomethylation	2005	<a href="#">More..</a>
arteriosclerosis	MCT3	Inactivation of monocarboxylate transporter MCT3 by DNA methylation in atherosclerosis	hypomethylation	2005	<a href="#">More..</a>
arteriosclerosis	ADOE	Plasma S-Adenosylhomocysteine is a better biomarker of atherosclerosis than homocysteine in apolipro	hypomethylation	2008	<a href="#">More..</a>

Details for this article ->->	
	PubMed ID : 9312159
Disease :	arteriosclerosis
Related Gene :	P21ras
Pathogenic Site :	vascular endothelial cells
Inducing Factor :	hmcysteine
Pathogenic Result :	vascular endothelial cells damage
Experiment Samples :	umbilical vein endothelial cells &aortic endothelial cells
Sample Species :	human
Methylation Sites :	P21 C17,C18,C20,C37
Pathway Description :	homocysteine decreased the methylation of P21ras, then the P21ras-MAP kinase activity decreased, then makes vascular endothelial cells damage.
<a href="#">ChainMap...</a>	

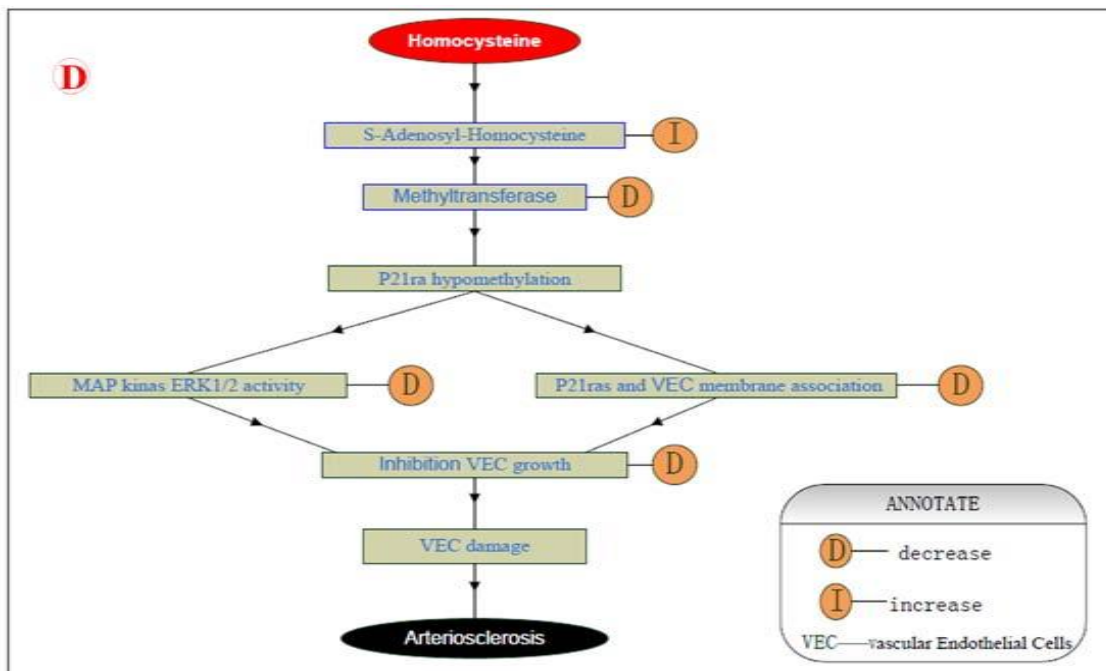


Fig. 1. The interface of dbDMAD.

(A) Search page. It can be searched by disease name or related gene.

(B) Result page for search. It provides a list of basic article information.

(C) A part of an example detail record. In the top of this page there has a hyperlink to PubMed web. In the below has a ChainMap button.

(D) An example of ChainMap page which shows the arteriosclerosis nosogenetic pathway.

#### 4. Database Implementation

dbDMAD is running on an Apache Tomcat web server and a MySQL server. The front page was built using PHP. Maps in the ChainMap page were drawn by Microsoft Office Visio 2007.

#### 5. Discussion and Future Development

In order to provide a central resource for biologists in the human aged disease research, we developed dbDMAD, a database system aimed at providing a comprehensive resource of DNA methylation information and their relationships to kinds of aged disease. The goal of the dbDMAD database project was to construct a platform for DNA methylation in human aged disease that would be interrelated with each other. In order to help users to see the pathogenic pathway in each search result, we developed a visualization tool ChainMap. In the future, we will add a tool which can find out the same factor in different maps. In this way, users may chase down the contact of different human aged diseases easily.

There are four databases about methylation that have been reported in publication. The first is HHMD, which focuses on the histone modification [9]. The second is methDB, which stores information about DNA methylation

data from experimental procedure [10]. The third is PubMeth, which focuses on the publish articles about the methylation information [11], and the last is MethyCancer, which includes the human DNA methylation and cancer information [12]. Table1 shows the detailed information about these four databases and lists every database concerns and special tools information for comparison.

Table 1. Atabase Comparative Information

DATABASE	CONCERNS	SPECIAL TOOLS
HHMD	Histone modification, including histone methylation information	HisModView: can show the histone modification map
MethDB	DNA methylation, including sample information and experiment information	On-line submit system[13]:allows public to directly enter new data into MethDB. Distributed Annotation System[14]:allows the epigenetic data sored in MethDB into the network of biological database.
dbDMAD	DNA methylation in human aged disease information.	ChainMap: can show the pathogenic pathways.
PubMeth	The publish articles of DNA methylation	None
MathyCancer	The relationship between DNA methylation and cancer.	CGPi130[15]: predicte the CpG islands methylation states.

Nowadays, the data volume in our database is smaller than MethDB or HHMD, but in the future we will increase more kinds of human aged disease. The data about DNA methylation status can help us to establish a predicting machine which can help to predict the other DNA methylation states which hasn't detected before. Like MethyCancer CGI prediction tools, we will develop tools to predict the CpG islands segments' methylation states.

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