

## Spatial distribution patterns of anorectal atresia/stenosis in China: Use of two-dimensional graph-theoretical clustering

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### Abstract

**AIM:** To investigate the spatial distribution patterns of anorectal atresia/stenosis in China.

**METHODS:** Data were collected from the Chinese Birth Defects Monitoring Network (CBDMN), a hospital-based congenital malformations registry system. All fetuses more than 28 wk of gestation and neonates up to 7 d of age in hospitals within the monitoring sites of the CBDMN were monitored from 2001 to 2005. Two-dimensional graph-theoretical clustering was used to divide monitoring sites of the CBDMN into different clusters according to the average incidences of anorectal atresia/stenosis in the different monitoring sites.

**RESULTS:** The overall average incidence of anorectal atresia/stenosis in China was 3.17 per 10000 from 2001 to 2005. The areas with the highest average incidences of anorectal atresia/stenosis were almost always focused in Eastern China. The monitoring sites were grouped into 6 clusters of areas. Cluster

1 comprised the monitoring sites in Heilongjiang Province, Jilin Province, and Liaoning Province; Cluster 2 was composed of those in Fujian Province, Guangdong Province, Hainan Province, Guangxi Zhuang Autonomous Region, south Hunan Province, and south Jiangxi Province; Cluster 3 consisted of those in Beijing Municipal City, Tianjin Municipal City, Hebei Province, Shandong Province, north Jiangsu Province, and north Anhui Province; Cluster 4 was made up of those in Zhejiang Province, Shanghai Municipal City, south Anhui Province, south Jiangsu Province, north Hunan Province, north Jiangxi Province, Hubei Province, Henan Province, Shanxi Province and Inner Mongolia Autonomous Region; Cluster 5 consisted of those in Ningxia Hui Autonomous Region, Gansu Province and Qinghai Province; and Cluster 6 included those in Shaanxi Province, Sichuan Province, Chongqing Municipal City, Yunnan Province, Guizhou Province, Xinjiang Uygur Autonomous Province and Tibet Autonomous Region.

**CONCLUSION:** The findings in this research allow the display of the spatial distribution patterns of anorectal atresia/stenosis in China. These will have important guiding significance for further analysis of relevant environmental factors regarding anorectal atresia/stenosis and for achieving regional monitoring for anorectal atresia/stenosis.

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**Key words:** Spatial distribution; Anorectal atresia/stenosis; Two-dimensional graph-theoretical clustering; Incidence; Monitoring

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## INTRODUCTION

Anorectal atresia/stenosis is a congenital malformation characterized by absence of continuity of the anorectal canal or of communication between rectum and anus, or narrowing of anal canal, with or without fistula, to neighboring organs<sup>[1]</sup>. Its incidence is rated high amongst gastrointestinal tract malformations. Incidence relates not only to genetic factors but also to environmental factors, especially spatial differences. There is, however, very little information available in literature about the spatial distribution patterns of anorectal atresia/stenosis in China.

Since 1986 China has been using the hospital-based Chinese Birth Defects Monitoring Network (CBDMN) to dynamically monitor severe congenital malformations such as anorectal atresia/stenosis<sup>[2]</sup>. We conducted this research to divide monitoring sites of the CBDMN into different clusters using two-dimensional graph-theoretical clustering analysis of the incidences of anorectal atresia/stenosis. Consideration was given to the similarities of the incidences of anorectal atresia/stenosis and the adjacent spatial relationships among different monitoring sites. This paper will present the spatial distribution patterns of anorectal atresia/stenosis and hopes to provide clues for research on its etiology.

## MATERIALS AND METHODS

### Objects

Research subjects were all perinatal fetal births more than 28 wk of gestation and neonates up to 7 d of age monitored in hospitals in the monitoring sites of the CBDMN from 2001 to 2005. They included live births, fetal deaths, stillbirths and those neonates who died within the first 7 d in these hospitals.

### Monitoring hospitals

Using the hospital-based guidelines for monitoring birth defects in developing countries, as recommended by World Health Organization (WHO), the CBDMN gathered data from about 460 hospitals in this hospital-based network. These hospitals - all of them above the county level - were located in 138 cities (138 monitoring sites) of 31 different provinces, municipal cities, and autonomous regions in China. The selection of monitoring sites used the method of stratified sampling based on the combination of geographical location, economic development level and infant mortality rate. The spatial distribution of monitoring sites is in accordance with the distribution of nationwide births. The nationwide program covers approximately 450 000-500 000 births annually through all monitoring hospitals.

### Information collection

The monitoring staff all received technical training on the case ascertainment of birth defects and the reporting of register forms. The monitoring hospitals collected the basic monthly information about the fetuses and

neonates from units of delivery, pediatric and pathology quarterly reports and filled in the "Quarterly Form for Perinatal Births". The monitoring staff in these hospitals filled in the "Registration Card for Births with Congenital Malformations" regarding the cases of diagnosed anorectal atresia/stenosis. All the forms were required to be handed over to the provincial birth defects monitoring offices; these would be reported to the National Center for Birth Defects Monitoring after scrutiny. The specific monitoring methods and quality control measures complied with those in reference<sup>[3]</sup>.

### Inclusion and exclusion criteria

The perinatal births diagnosed as having anorectal atresia/stenosis with reference to criteria in Code Q42.1 and Code 42.3 in ICD-10 were included in this research. According to the criteria authorized by the International Clearing house for Birth Defects Surveillance and Research (ICBDSR), cases of mild stenosis which did not need correction and ectopic anus were excluded.

### Spatial distribution analysis

The Excel Package was used to build the database of data of anorectal atresia/stenosis by monitoring sites. The ArcView GIS 3.2 was applied to spatially display the average incidences of anorectal atresia/stenosis in different provinces, municipal cities, and autonomous regions.

### Two-dimensional graph-theoretical clustering:

The graph is a set of vertices and edges that connect pairs of vertices in the space<sup>[4-6]</sup>. According to the basic requirements for clustering the two-dimensional ordinal samples, the similarities of the disease-related variables between members of the same cluster and their disparities between members of different clusters need to be maintained. The connectivity of the geographic units within the cluster also needs to be conserved. The weighted connected graph was supposed to be  $G = (V, E, D)$ , in which (1)  $V$  represents the set of the locations of the geographic units (referred to monitoring sites in this research), (2)  $E$  represents the initial location connection matrix  $B^{(0)}$  (Formula 1), the set of the adjacent relationships among different monitoring sites, and (3)  $D$  represents the initial disease-related distance matrix  $D^{(0)}$  (Formula 2), the weights between different vertices in the tree algorithm in the graph theory. Based on the weighted connected graph  $G = (V, E, D)$ , minimum spanning trees (MST) which were of biogeographic significance<sup>[7,8]</sup> were constructed by the Kruskal MST algorithm<sup>[9]</sup>. The two vertices with the minimum distance measures were selected and connected. One of the remaining vertices was selected and connected with the one of the two connected vertices to which it showed the minimum distance measured. The other remaining vertices were connected consecutively with those vertices already connected in the same manner until all the vertices were interconnected. The whole process was completed by the DPS7.05 software package<sup>[10]</sup>.

$$B^{(0)} = (b_{ik}^{(0)})_{n \times n}; \quad i, k = 1, 2, \dots, n \quad (\text{Formula 1})$$

$$D^{(0)} = (d_{ik}^{(0)})_{n \times n}; \quad i, k = 1, 2, \dots, n \quad (\text{Formula 2})$$

Where  $b_{ik}^{(0)}$  is the labeling of location connection between the monitoring site  $i$  and the monitoring site  $k$ . The value of  $b_{ik}^{(0)}$  is 1 if the two monitoring sites are adjacent, while it is 0 when the two monitoring sites are not.  $d_{ik}^{(0)}$  is the similarity distance between the incidence of the monitoring site  $i$  and that of the monitoring site  $k$ .

The MST was deconstructed by the method of “necks” in the graph theory<sup>[11]</sup>. Specific steps processed were as follows: (1) calculating the “branches”: All  $n$  vertices were interconnected by  $(n-1)$  edges. Two of these vertices were connected only by one edge and the others were connected by at least two edges, which thus formed a chain without circuits, called the “branch”. The branch with the most edges was called the main branch (or diameter) of the MST; (2) calculating the “subsidiary main branch”. Starting from any vertex in the main branch of MST, the branch with the most edges, other than the main branch, was separated out and called the subsidiary main branch. The number of edges of the subsidiary main branch was called the “depth” of the vertex; (3) identifying “necks”. The task was twofold: (I) to appoint an integer “ $a$ ” (that is  $> 1$ ), and (II) to find the subsidiary main branch of every vertex with a depth  $\geq a$  in the main branch. The edges, which connected the vertices with the depth of 0 in the main shared parts of every subsidiary main branch, were called the “neck”; and (4) the necks were deleted in the graph to deconstruct the MST into parts so that the monitoring sites in the graph were divided into different clusters accordingly.

The layer of the deconstructed MST was added to the Administrative Boundary Layer of the 1:4M-scale Topographic Database of the National Fundamental Geographic Information System of China to formulate the two-dimensional MST-based cluster graph. The clustering results were used to make another cluster map for visual observation. This process was performed by the ArcView GIS 3.2 package software.

## RESULTS

A total of 2 670 367 perinatal births were monitored from 2001 to 2005 all over China. Eight hundred and forty six cases of anorectal atresia/stenosis were found, equating to a total average incidence of 3.17 per 10 000. See Table 1 for the average incidences of anorectal atresia/stenosis in different provinces, municipal cities or autonomous regions. The top five incidences appeared in Liaoning (4.89 per 10 000 births), Zhejiang (4.83 per 10 000 births), Guangdong (4.78 per 10 000 births), Chongqing (4.59 per 10 000 births) and Beijing (4.10 per 10 000 births).

### Spatial distribution

Regarding the geographic division standard for Eastern,

Table 1 Average incidences of anorectal atresia/stenosis in different provinces, municipal cities or autonomous regions of China from 2001 to 2005

Province/Autonomous region/Municipal city	Perinatal births	Cases	Average incidence (per 10 000)
Liaoning	79 760	39	4.89
Zhejiang	111 690	54	4.83
Guangdong	127 648	61	4.78
Chongqing	60 979	28	4.59
Beijing	114 741	47	4.10
Guangxi	64 444	26	4.03
Tianjin	62 542	25	4.00
Anhui	100 631	36	3.58
Fujian	95 970	34	3.54
Ningxia	65 064	23	3.53
Jiangsu	149 984	52	3.47
Jilin	112 606	38	3.37
Shanxi	76 653	24	3.13
Henan	126 082	39	3.09
Hubei	59 964	18	3.00
Hebei	130 441	39	2.99
Gansu	61 629	18	2.92
Hunan	85 919	25	2.91
Heilongjiang	71 224	20	2.81
Hainan	54 234	14	2.58
Shandong	164 141	42	2.56
Guizhou	58 695	15	2.56
Sichuan	88 783	22	2.48
Shanghai	144 361	34	2.36
Inner Mongolia	63 061	14	2.22
Yunnan	85 398	17	1.99
Jiangxi	84 015	15	1.79
Xinjiang	56 214	10	1.78
Shaanxi	64 634	11	1.70
Qinghai	36 666	6	1.64
Tibet	12 194	0	0.00
Total	2 670 367	846	3.17

Middle and Western China from the National Bureau of Statistics of China in 2003<sup>[12]</sup>, the areas (provinces, autonomous regions, or municipal cities) with the highest average incidences of anorectal atresia/stenosis were concentrated in Eastern China, while the areas with the lowest average incidence of less than 1.99 per 10 000 were mostly located in Western China (Figure 1).

### Results of the two-dimensional graph-theoretical clustering

The MST was constructed with consideration to the similarities of average incidences of anorectal atresia/stenosis and the spatial connectivity between different monitoring sites (Figure 2). According to the “neck” calculation method in the graph theory, when the integral constant,  $a$ , was designated as 2, the monitoring sites were divided into 6 clusters of different areas.

Regarding the average incidences of anorectal atresia/stenosis in different provinces, municipal cities and autonomous regions from 2001 to 2005, the monitoring sites were grouped into 6 clusters. Cluster 1 comprised the monitoring sites in Heilongjiang Province, Jilin Province, and Liaoning Province; Cluster 2 was composed of those in Fujian Province, Guangdong Province, Hainan Province, Guangxi Zhuang Autonomous Region, south Hunan Province,

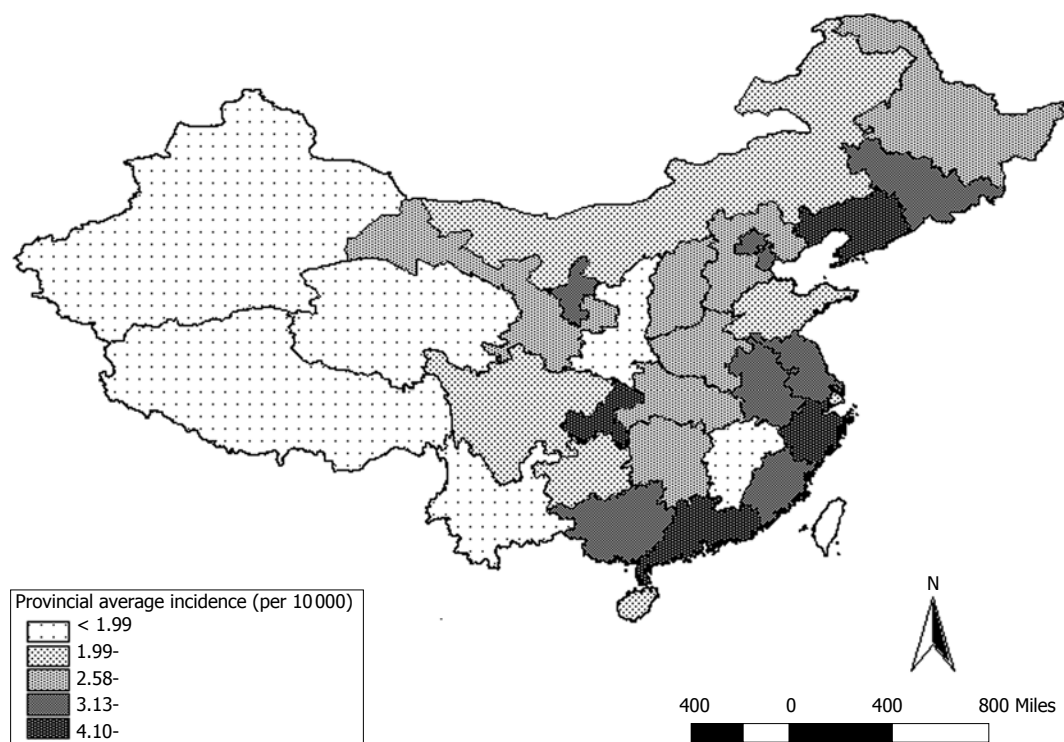


Figure 1 National distribution graph of average incidences of anorectal atresia/stenosis in different provinces, municipal cities and autonomous regions from 2001 to 2005.

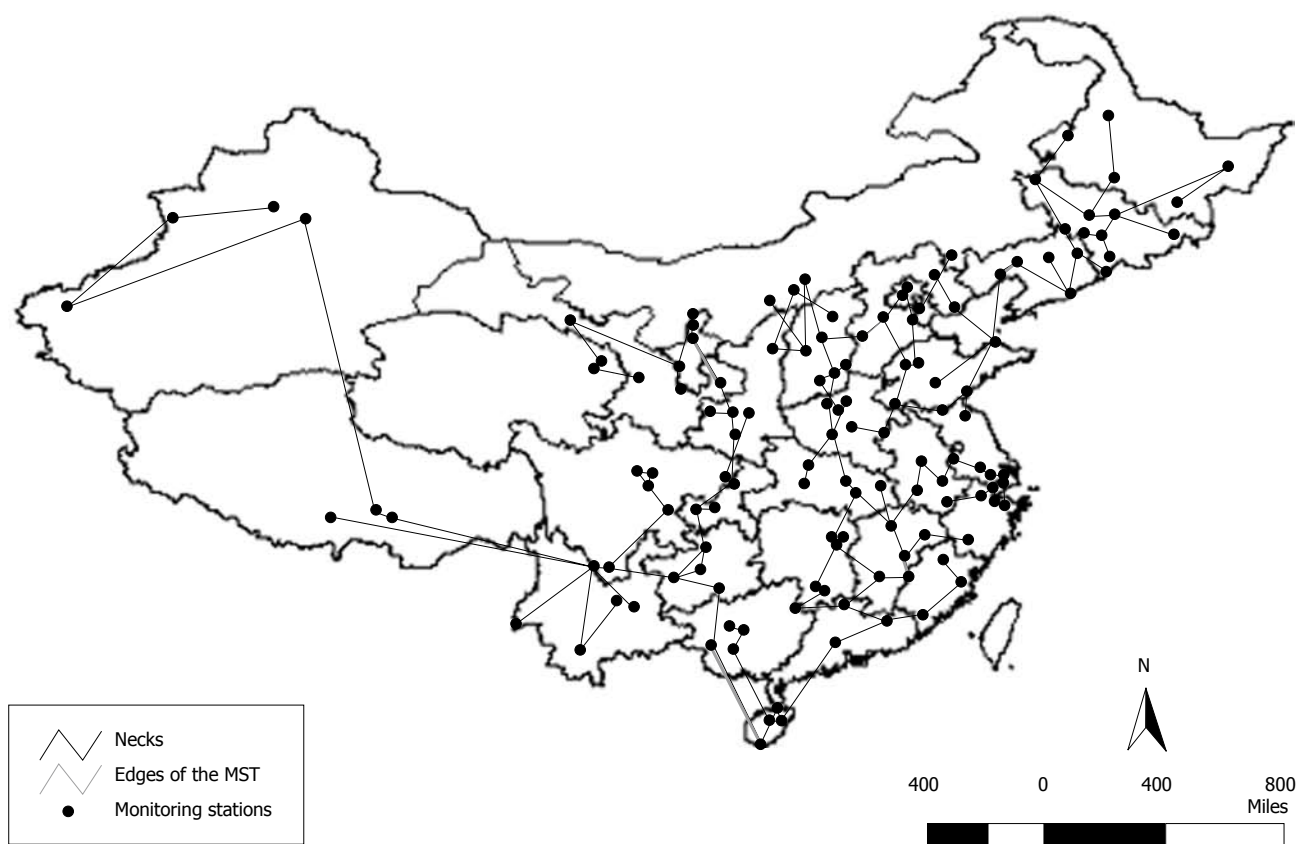


Figure 2 Two-dimensional MST-based cluster graph of monitoring sites in China from 2001 to 2005.

and south Jiangxi Province; Cluster 3 consisted of those in Beijing Municipal City, Tianjin Municipal City, Hebei Province, Shandong Province, north Jiangsu Province,

and north Anhui Province; Cluster 4 was made up of those in Zhejiang Province, Shanghai Municipal City, south Anhui Province, south Jiangsu Province,



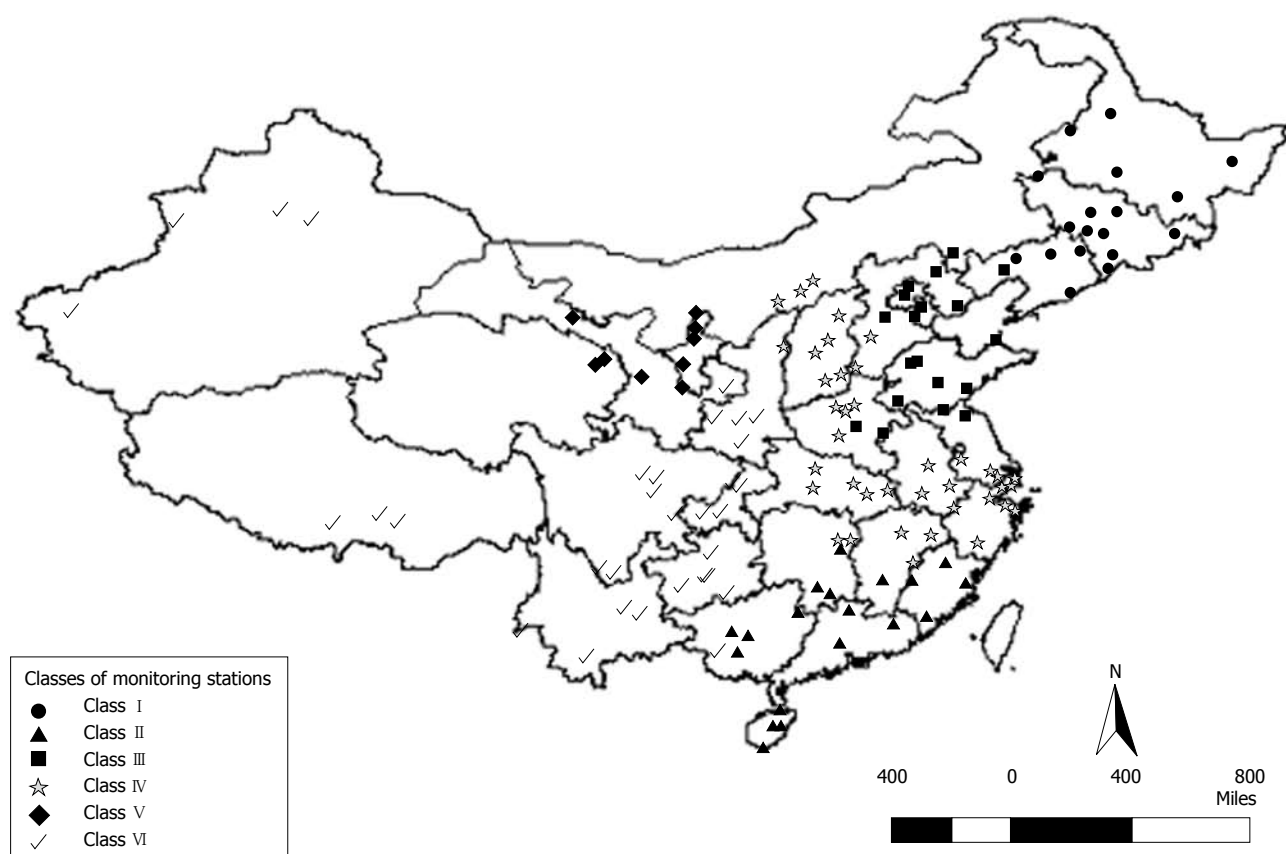


Figure 3 Cluster graph of monitoring sites in China from 2001 to 2005.

north Hunan Province, north Jiangxi Province, Hubei Province, Henan Province, Shanxi Province and Inner Mongolia Autonomous Region; Cluster 5 consisted of those in Ningxia Hui Autonomous Region, Gansu Province and Qinghai Province; and Cluster 6 included those in Shaanxi Province, Sichuan Province, Chongqing Municipal City, Yunnan Province, Guizhou Province, Xinjiang Uygur Autonomous Province and Tibet Autonomous Region (Figure 3).

## DISCUSSION

Anorectal atresia/stenosis is one of the most common malformations in the gastrointestinal tract. Due to pathological changes in the anus and rectum, one-third of the perinatal births with anorectal atresia/stenosis suffer from defecation difficulties of varying degrees of severity following surgery. Most of these births need life-long treatment that severely compromises the quality of life and psychological development in particular. This situation is a burden not only to these babies, but also to their entire families and even to society as a whole in China<sup>[13-17]</sup>. Some researchers<sup>[18-22]</sup> suggested that mothers' contact (when they are pregnant) with environmental pollutants could increase their risk of giving birth to babies having congenital malformations. The current research found that the areas with the highest incidences of anorectal atresia/stenosis were concentrated in Eastern China, especially in Liaoning, Zhejiang and Guangdong. With a solid industrial and agricultural base,

economic conditions in Eastern China flourish. Most manufacturing plants and industrial factories (including marine-aquatic industries) are located in Eastern China. It is known that these factories are responsible for water pollution and other industrial pollution at a level that is deemed severe. Perhaps mothers in Eastern China have babies with more congenital malformations because of the mothers' severe exposure to these physical and chemical pollutants when they are pregnant. In addition, the regional differences in awareness and uptake of available health care for pregnant woman, infrastructure of monitoring hospitals and diagnosis at a technical level were also factors likely to explain some of the observed geographical variation in anorectal atresia/stenosis. In Western China, limited at economic and cultural levels, most pregnant woman have weak awareness and uptake of health care, which means they do not actively seek antenatal care, so there is the probability of under-reporting of cases, resulting in the lower incidence. As to the health services, in the less developed western regions, the maternal and child healthcare facilities may lack necessary infrastructure, and the technical levels of monitoring staff may be limited, which may also result in the lower detection of congenital malformation.

Cluster analysis is an exploratory data analysis tool for solving classification problems. Assuming the samples as the vectorial points in hyperspace, the object of cluster analysis is to sort the samples into clusters so that the degree of association is strong between members of the same cluster and weak between members of different

clusters. It has widespread application because of its advantage of definite classification. In analysis of spatial distribution structures of disease, both the similarities and the adjacent relationships of geographic units of the same cluster are of interest to researchers<sup>[23]</sup>. The traditional cluster analysis cannot meet all the requirements. Nevertheless, the two-dimensional graph-theoretical clustering model systematically (1) combines the concept of the two-dimensional constrained spatial hierarchical clustering and the MST method in the graph theory; (2) utilizes the spatial analysis measures of Geographic Information System (GIS) in combination with the tree algorithm to divide the geographic units into clusters. This model allows researchers to consider the similarities as well as the spatial connectivity between different units in the same cluster. This is of significance in (1) analyzing the similarities of different geographic units, (2) demonstrating the spatial distribution of the disease, and (3) identifying the boundaries of the spatial heterogeneity of the disease. Luo *et al*<sup>[24]</sup> combined the principal component analysis and two-dimensional graph-theoretical clustering to identify the evaluation method for land consolidation priority. Cao *et al*<sup>[25]</sup> divided the national corn reserve regions based on the two-dimensional graph-theoretical clustering, providing references for application of regional corn reserve technology and for the formation of guidelines for macro-regional corn reserve technology. Few researchers, however, have reported on the use of two-dimensional graph-theoretical clustering as applied to study the spatial distribution of congenital malformations.

This research utilized the two-dimensional graph-theoretical clustering to divide monitoring sites of the CBDMN into different clusters of areas based on average incidences of anorectal atresia/stenosis. The findings in this research will have important guiding significance for further analysis of relevant environmental factors regarding anorectal atresia/stenosis and for allowing regional monitoring for anorectal atresia/stenosis. On the one hand, the congenital malformations relate not only to genetic factors, but also correspond with the influence of other conditions: geographic environment, climate, economic development and even cultural development<sup>[26-30]</sup>. The results from the two-dimensional graph-theoretical clustering will enable epidemiologists to determine which environmental factors affect the incidence of anorectal atresia/stenosis in each cluster of areas by considering their respective environmental characteristics. On the other hand, although these data showed high incidence of anorectal atresia/stenosis in Eastern China and low incidence in Western China, it is true that different areas within Eastern China and Western China have their own demographic, economic and environmental characteristics. Large-scale monitoring cannot obtain detailed influential factors of anorectal atresia/stenosis in any given region. The results in this research provide an approach for researchers to monitor relevant environmental influential factors for incidence of anorectal atresia/stenosis regionally. By dividing the

monitoring sites of the CBDMN into different clusters, the detailed relevant environmental risk factors for anorectal atresia/stenosis in different geographic units can be collected within the same cluster to allow regional monitoring.

The current research took account of the adjacent relationship between different monitoring sites rather than different provinces, autonomous regions or municipal cities, which guaranteed the requirements for geographic divisions for this study. However, if different monitoring sites in the same province were incorporated into different clusters after two-dimensional graph-theoretical clustering, the monitoring work at the provincial level would be subjected to increased difficulties.

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## COMMENTS

### Background

The incidence of anorectal atresia/stenosis is high amongst gastrointestinal tract malformations. It relates not only to genetic factors but also to environmental factors, especially spatial differences. However, very little information available in literature about the spatial distribution patterns of anorectal atresia/stenosis in China.

### Innovations and breakthroughs

This is the first study to report the spatial distribution of anorectal atresia/stenosis in China using two-dimensional graph-theoretical clustering considering simultaneously the similarities as well as the spatial connectivity between different units in the same cluster.

### Applications

The findings will have important guiding significance for further analysis of relevant environmental factors of anorectal atresia/stenosis and for allowing regional monitoring for anorectal atresia/stenosis.

### Terminology

Anorectal atresia/stenosis: a congenital malformation characterized by absence of continuity of the anorectal canal or of communication between rectum and anus, or narrowing of anal canal, with or without fistula to neighboring organs.

Two-dimensional graph-theoretical clustering: a cluster method of combining the concept of the two-dimensional constrained spatial hierarchical clustering and the MST method in the graph theory, and utilizing the spatial analysis measures of geographic information system (GIS) in combination with the tree algorithm to divide the geographic units into clusters.

### Peer review

The study is based on 460 hospitals from 138 cities across China, and is an interesting paper on the geographical distribution of anorectal atresia/stenosis across China.

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