

A Survey of Epidemiological Studies and Risk Factors of ASD, with a Focus on China

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Autism spectrum disorder (ASD) is a group of pervasive developmental disorders which usually first appear in childhood. ASD was considered rare in the past, however, it has become a relatively common disease with a dramatic increase of prevalence recently. For years, epidemiological studies for ASD were carried out in many countries and relevant methodologies for investigation have become comparably mature. By the contrary, only a few epidemiological studies for ASD have been completed in China, involving only a small portion of China's vast population. So far, many explanations for the increased prevalence have been proposed, and yet these studies are almost exclusively conducted in the western world. Research suggests that some environmental risk factors, which may interact with susceptible genes, are likely to play a role in the etiology of ASD. ASD exerts great burden on affected families and the society. Therefore, it's vital to better define ASD prevalence and understand its risk factors in different regions of the world, in order to help prevent, diagnose and treat this group of diseases.

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INTRODUCTION

Autism spectrum disorders (ASD) is a group of developmental disorders that occur in early childhood. According to the International Classification of Diseases Manual (ICD-10) and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), they include autistic disorders, childhood disintegrative disorder, Asperger syndrome (AS), or pervasive developmental disorders-not otherwise specified (PDD-NOS). ASD is characterized by social communication deficits, fixated interests and repetitive behaviors. For most affected children the symptoms appear before 3 years of age, and ASD affects more males than females.¹⁻⁴ The severity of ASD varies. In less severe patients, their language ability is better than average ASD individuals, and they only have mild social difficulties; however, in severe cases they may not speak for life.⁵ ASD patients often present with various related comorbidities, which include epilepsy, anxiety disorder, intellectual abnormalities, self-injury, obesity/overweight,

inflammatory bowel disease, atopic dermatitis, sensory disorders, and so on.⁶⁻¹³

ASD was considered a rare disease before the 1980s, with a prevalence of less than 5/10000, whereas studies after the 1990s found an increasing trend in ASD prevalence. In recent years, ASD prevalence rate is estimated to be 1% ~ 2%, with some studies proposing as high as 6%.¹⁴ Many factors were thought to contribute to the significant increase of ASD prevalence, such as widening diagnostic criteria, early diagnosis of the age, awareness of parents and public, pathogenic genes and so on.¹⁴ At the same time, environmental risk factors have gradually become a hotspot of research focus, as epidemiological and molecular biology studies have found many possible environmental risk factors associated with ASD. Although the specific mechanisms are still elusive, many agree that the effects of environmental factors on ASD cannot be ignored.¹⁵

In this paper, we will review the progress of epidemiological surveys of ASD, and studies on environmental risk factors in recent 30 years, with a focus of the situation of ASD in China. Studies exploring genetic/environmental risk factors of ASD were almost exclusively conducted in the Western world,

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which highlights the needs for further investigation under a global health framework.

ASD PREVALENCE

Progress of International ASD Epidemiological Survey

Before the 1980s, ASD epidemiological surveys mainly focused on autism, and the prevalence rate was 0.5% or less, so autism was considered a rare disease. Since the 1980s diagnostic criteria for autism began to change, and epidemiological surveys extended from autism to ASD (including PDD). Because of the discrepancy in investigation purposes, difference between "ASD" and "autism" definition, various case selection criteria and diagnostic criteria, and different methods of the epidemiological surveys, the results of epidemiological studies vary widely. Nonetheless, the measured prevalence rates of ASD overall have been greater than 0.5% with an upward trend in many countries.¹⁶

With the advent of consistent diagnostic criteria, recent studies have focused on ASD or autistic disorder, which is the most serious subgroup of ASD.⁷ In the United States, autism and developmental disorders monitoring network (ADDM), which was established in 2000 in the United States, reported that the prevalence of ASD in children aged 8 years in the United States in 2000, 2002, 2006, 2008, 2010 and 2012 was 6.7‰, 6.6‰, 9.0‰, 1.13%, 1.47% and 1.46% respectively.¹⁷⁻²² The prevalence of ASD was 1.1% in a survey of children aged 3 to 17 years in USA by phone interview in 2009.²³ A 15~20 year time period examination found that the prevalence of ASD in 8-year old children increased by 2.69 fold in Atlanta of USA (from 4.2‰ in 1996 to 15.5‰ in 2010).²⁴ ASD gradually became second in all severe developmental disorders just after mental retardation. An epidemiological study of school children in Canada under the age of 18 found that the prevalence of ASD was more than 6.0 per thousand.²⁵ In 2006, in a UK survey, the prevalence of ASD in children aged 9 to 10 in the United Kingdom reached 1.16% and the prevalence of autism was 3.89%.²⁶ In France, about 3.65% 7-year old kids were diagnosed ASD, and the prevalence increased through 1997 to 2003.²⁷ In Sweden, the prevalence of ASD among individuals aged 2~17 years increased from 0.42% in 2001 to 1.44% to 2011.²⁸ A Danish cohort analysis also showed a gradual increase in the prevalence of ASD and autism as well.²⁹ In a cross-sectional study in Lebanon, about 1000 children were investigated, and around 1.51% were diagnosed as ASD using M-CHAT (Modified checklist for autism in toddlers) screening. In Ecuador the prevalence of ASD was 0.32%.³⁰

Ratio of the prevalence between males and females with ASD and autism varied significantly in epidemiologic studies, with an average of 3~6:1. Furthermore, the disease is usually much more severe in males than in females.^{17-22,24} In 2007, an epidemiological survey of adult ASD was conducted in the UK, and the prevalence of adult ASD was similar to that of children, indicating that the prevalence of ASD in adults was not elevated.³¹

In summary, the prevalence rates of ASD and autism in

different countries and regions vary widely, but the increasing trend worldwide is consistent.

Progress of ASD Epidemiological Survey in China

The epidemiological investigation of ASD in China began in the 1990s. So far there is no nationwide epidemiological data, and limited surveys or investigations all focused on autism instead of ASD. The scope and sample sizes of these studies were limited as well. A multi-site epidemiological survey carried out in six provinces and cities, which investigated children with disabilities, determined that the prevalence of autism was 1.01 ‰.³² In other local surveys the prevalence of autism ranged from 0.29% to 1.80%.³³⁻³⁸ There are few surveys on ASD. In 2004, 0-6 year-old children in Beijing were investigated, and the prevalence of PDD was 1.53%.³²

According to a survey in Hong Kong in 2008, the prevalence of ASD was 1.61%.³⁹ In Shanghai, over 10,000 children aged 4~6 years old were surveyed, and the prevalence of ASD was only 0.93%.⁴⁰ As mentioned above, the reported prevalence of ASD and autism in China was less than the internationally reported values. However, in a recent epidemiological study, which took advantage of a new screening and diagnostic instrument comparable to that used in the western countries, the reported prevalence of ASD in Beijing was 1.19%, which was similar to that of developed countries, indicating that an effective and comparable method should be established for the investigation or diagnosis of ASD in China.⁴¹ Due to the lack of high-quality, large-scale epidemiological data, the current trend of ASD or autism in China cannot be systematically analyzed.

Hypotheses of the Rising Prevalence of ASD

Since the 1980s, the prevalence of ASD has increased significantly, but whether the incidence of ASD is truly rising is still controversy.¹⁴

The increase of ASD prevalence has been partially attributed to the widening of diagnostic criteria. Some epidemiological studies surveyed both ASD and other psychiatric diseases, and found that the prevalence of the latter declined while the prevalence of the former rose. Therefore it was inferred that the rise of ASD prevalence rate may be due to the fact that the cases that were not diagnosed as ASD were classified as ASD because of changes in diagnostic criteria, suggesting that the incidence of ASD may not have truly risen.^{42,43} However, some studies have not found this phenomenon to be true.⁴⁴

Second, a recent Danish study reported that the age of autism and ASD diagnosis dropped, resulting in an increase in prevalence. However, the follow-up time of the study is too short to determine whether the increase in the prevalence of ASD is due to increased incidence.²⁹

Increased social concerns and public awareness can also contribute to this phenomenon to a certain extent. Surveillance and follow-up of the special education population, combined with increased public awareness, have led to an increase in the number of diagnoses and disease prevalence.^{29,45}

Meanwhile, we cannot rule out the possibility that incidence of ASD and autism truly increased. New genetic and environmental risk factors associated with ASD have been identified continuously, which may contribute to increased prevalence of ASD.⁴⁶ In support of this idea, an epidemiologic study of ASD in California, United States, concluded that the prevalence of ASD was increased after excluding confounding factors affecting the prevalence of ASD, such as population migration and diagnostic criteria.

INFLUENCE OF ENVIRONMENTAL FACTORS ON ASD

The increasing trend of ASD prevalence in recent years has alarmed the public and the medical community.¹⁵ ASD is recognized as one of the most severe developmental disorders. Multiple factors, such as genetic/genomic, epigenetic/epigenomic and environmental ones, are thought to be necessary for the pathogenesis of autism. To date, hundreds to thousands of causative and susceptible genes, copy number variants (CNVs), rare de novo mutations (SNVs) and common SNPs, as well as microRNAs have been associated with ASD. However, those genetic factors could only explain the pathogenesis of approximately 25% of ASD, and the remaining 75% are unknown. It has been proposed that ASD is a complex disorder (aka multi-factorial disease) caused by the interaction between genes and environmental factors. The genetic background of individuals determines their susceptibility, and susceptible individuals can develop ASD under specific environmental conditions.¹⁵ Environmental factors, susceptibility genes and specific times of exposure may be the three essential conditions for the onset of ASD. While recent reviews have provided further insight into the genetic basis of ASD,^{47,48} we will review the evidence of environmental risk factors and relevant epigenetic mechanisms, including DNA methylation, chromatin factors and long non-coding RNAs, in the pathogenesis of ASD. These studies are almost exclusively performed in the western world, which highlights the need for parallel investigations/analyses of known risk factors in China and the need to exploring novel risk factors that are country-specific.

Environmental Factors

Environmental exposures have been widely accepted as important risk factors in autism etiology. Accumulating evidence also shows that these exposures interplay with known ASD candidate genes.⁴⁷ Epidemiological and toxicological studies have found a variety of environmental risk factors associated with ASD, mainly heavy metals, teratogenic drugs, maternal infection and antibodies, pesticides and harmful air pollutants; others such as nicotine, alcohol, have been reported, but their association with ASD needs to be verified.⁴⁹

Heavy metals and ASD

Mercury is one of the most thoroughly studied environmental factors that may be associated with ASD. Mercury is widely distributed in the form of elemental mercury, inorganic mercury and organic mercury in plant-emitted mercury vapor, mercury-contaminated fish, mercury-containing drugs,

thimerosal-containing vaccines and dental fillers; and it can cross body's physiological barriers and reach the target site resulting in toxicity.⁵⁰ So far, although there are a lot of conflicting data on this topic, consensus is that there is no convincing evidence to support a role of mercury in the pathogenesis of ASD.

Thimerosal is an ethylmercury-containing disinfectant that has been used extensively in cosmetics, pharmaceuticals and vaccines since the 1930s, and particularly vaccines. Figure 1 shows the exposure of mercury to children within 18 months of birth in the United States since the 1980s,⁵¹ and it indicates that children in the United States were exposed to high levels of mercury through thimerosal mercury-containing vaccines in 1999. The hair and urine mercury content was detected in infants and young children who received planned immunization, and the testing values exceeded the thresholds of USA. Thus USA limited the use of thimerosal in vaccines,⁵² and by 2001 almost all vaccines did not contain thimerosal. However, since 2003, thimerosal containing DTaP vaccine, hepatitis B vaccine and Hib vaccine have been approved for use.

With the use of thimerosal in vaccines, the prevalence of ASD also appeared to change. A number of epidemiological studies have shown that thiomersal levels in vaccines are positively related to the prevalence of ASD, as shown in **Table 1**.

While there are several studies that support the hypothesis that thimerosal in vaccines is positively associated with ASD, other studies have rejected this view. For example, in 2003, Hviid et al. used a longitudinal epidemiologic survey to follow up on more than 14,000 Danish children and found no association between thimerosal and ASD;⁵⁶ American CDC retrospectively re-evaluated the safety of thimerosal-containing vaccines and found negative results as well. Although this study was controversial, the results suggest that the association between thimerosal in vaccines and ASD still needs further investigation;⁵⁷ in 2008, Schechter analyzed the prevalence of ASD among children of different birth cohorts in California from 1995 to 2007, and found that the prevalence was consistently increasing, contrary to the trend of decreasing mercury content in vaccines.⁵⁸ In addition, recent findings of ASD clustering have also questioned the association between vaccine mercury and ASD.⁵⁹

The mercury-containing vaccine that pregnant women are inoculated with is mainly Rho (D) immunoglobulin, which is one of the ways children are exposed to mercury before birth. In a prospective case-control (53 ASD children and 926 normal controls) study in 2007, Geier et al. found that there were more Rh-negative mothers in ASD group than in control (OR = 2.35, 95 % CI: 1.17 to 4.52).⁶⁰ However, in 2008, Croen et al.'s case-control study failed to repeat this result.⁶¹ In addition, mercury-containing dental fillings of the pregnant women can also be a source of intrauterine mercury exposure. Although epidemiological studies have shown the association of maternal use of mercury-containing filler during pregnancy with offspring of ASD, these studies are often not robust

enough due to the limitations of methodology. It has also been reported that mercury in the environment may be associated with ASD. In a survey of nearly 4 million children in 254 towns in Texas, Palmer et al. found that the prevalence of ASD would increase by 61% for every 1000 pounds of mercury release from the environment;⁶² but this was an ecologically study with its own limitations of methodology.

In addition to the studies above, molecular epidemiological studies also analyzed the association between ASD with mercury. Bradstreet et al. took the amount of urine mercury as a marker of mercury load in the individual body, and found that the urinary mercury increased in ASD group by 3.15 fold compared with control, suggesting a high mercury load (<http://www.progressiveconvergence.com/>). Geier studied 28

children with ASD and found that the urinary porphyrin content and the severity of disease was positively correlated.^{63,64} Nevertheless, Hertz-Picciotto did not find the association of blood mercury with ASD.⁶⁵ On the other hand, toxicological studies have reported that mercury poisoning resulted in the sensory, behavioral, neuroanatomical and biochemical abnormalities that were similar to the phenotype of ASD,⁶⁶ but that mercury itself is a neurotoxin cannot directly prove the association of mercury poisoning and ASD.

In summary, the association between mercury and ASD is not consistent across studies, and there is no convincing evidence to support their correlation.⁶⁷ Other heavy metal elements, such as lead, were studied as well, but these studies were also not robust enough to yield any conclusions.

Table 1. Epidemiological studies of the association between thimerosal and ASD.

Year	Method	Source	Conclusions	Authors
2003	Ecological research	United States VAERS * database	The risk of developing ASD thimerosal-containing DTaP vaccines was six times greater (RR = 6.0).	Geier M.R Geier D.A ⁵³
2003	Ecological research	United States VAERS * database	The prevalence of ASD increased by 1 million per 1 mg of mercury in vaccines. The risk of ASD increased exponentially with increasing exposure to thimerosal.	Geier M.R Geier D.A ⁵⁴
2006	Meta analysis	United States VAERS * database	The amount of mercury in the vaccine increased by 100µg, the risk of ASD is 1.56 times the normal, (OR = 1.56, 95% CI: 1.05 to 2.34), The risk of neurodevelopmental disorders (ND) is 1.61 times normal, (OR = 1.61, 95% CI: 1.27-2.05).	Geier M.R Geier D.A ⁵⁴
2008	Cohort Study	United States VAERS * database	The risk of childhood ASD and autism was 2.87 times higher (OR = 2.87, 95% CI: 1.19-6.94) and 2.62 times higher than that of the control group (OR = 2.62, 95% CI: 1.15 ~ 6.01); The risk of childhood ASD and autism was 2.44-fold (OR = 2.44, 95% CI: 1.16 to 5.10) and 2.20 fold (OR = 2.20, 95% CI: 1.10 to 4.40).	Young H.A Geier M.R Geier D.A ⁵⁵
2006	Ecological research	United States VAERS * database	Prevalence of ASD dropped after removal of thimerosal from vaccines	M.R Geier D.A Geier ⁵¹
2006	Ecological research	United States VAERS * and CDDS 3 database	The number of cases of ASD reported from 1994 to 2002 showed an increasing trend, which decreased from 2002 to 2005, indicating that the risk of ASD was decreased after thiomersal was removed from the vaccine.	Geier M.R Geier D.A [@]

*VAERS: Vaccine Adverse Event Reporting System; #VSD: Vaccine Safety Datalink; §CDDS: California Department of Developmental Service database; & <http://www.jpands.org/vol8no1/geier.pdf>; @ <http://www.jpands.org/vol11no1/geier.pdf>

Teratogenic drugs

At least three drugs, namely valproic acid (VPA), thalidomide, and misoprostol, have been found to contribute to a relatively small proportion of ASD.¹⁴

VPA is a commonly used antiepileptic drug, and many ASD cases have been reported to be VPA-related. Moore et al investigated 57 patients with fetal anticonvulsive syndrome. Among them 34 patients showed ASD-like traits, and 6 patients were diagnosed with ASD, 5 of whom were exposed to intrauterine VPA.⁶⁸ Rasalam et al. found 11 out of 260 children with long-term intrauterine exposure to anticonvulsant were diagnosed with ASD, and 9 of them had intrauterine exposure to VPA.⁶⁹ Rat or mouse ASD model can also be constructed with VPA exposure. The offsprings of rats which were exposed to VPA during gestation showed similar phenotypes of ASD, such as increased pain threshold,

repetitive stereotyped motion, abnormal coordination of complex motion, decreased Purkinje cells, small cerebellum, and abnormal distribution of 5-HT-nergic neurons in the dorsal raphe nucleus of the brain.⁷⁰⁻⁷²

Thalidomide (thalidomide) is a sedative with a strong teratogenic effect. Reexamination of 100 patients in the thalidomide event found that 4 of these patients had ASD, suggesting that thalidomide could adversely affect neural development and lead to ASD by maternal exposure to the drug at a critical period of embryonic nervous system development (embryonic day 20-24).⁷¹ However, the evidence is relatively weak given the small sample size.

Infection and immune abnormalities

For a long time, case reports and epidemiological studies have shown that maternal infection during pregnancy may be a risk

factor for ASD. From the seventies and eighties of the last century, there were reports suggesting that ASD was related to congenital rubella virus infection and congenital cytomegalovirus infection.⁷³ In recent years, a large number of animal experiments supported these hypotheses. Adult pregnant rats were infected with bacterial endotoxin (LPS), human influenza virus, viral analogues Ploy I:C or inflammatory cytokines, and it was observed that their offsprings developed ASD-like symptoms; and the effects was greater in the first trimester than in the third trimester.^{74,75}

As a special environmental factor, abnormal maternal immunoglobulin (mainly autoantibodies to certain proteins of fetus nervous system) can enter the fetal brain through the placenta, affecting the normal development of fetal nervous system, which may be one pathogenic mechanism of ASD.^{61,76} ⁷⁷ Braunschweig et al. found two abnormal anti-fetal brain antibodies weighing 37kDa and 73kDa. Antibodies with a molecular weight of 37kDa were more common in mothers with ASD children (OR = 5.69, 95% CI: 2.09-15.51). Furthermore, only in mothers with ASD children could these two antibodies be detected at the same time.⁷⁸ Martin et al. injected IgG from mothers of ASD and normal controls respectively into pregnant rhesus monkeys, and they found that offsprings of rhesus monkeys treated with the former showed abnormal ASD-like behaviors.⁷⁹

Other environmental risk factors

Besides those factors above, it has been reported that maternal autoimmune disease, obesity during pregnancy, and psychiatric disorders are all associated with ASD of offsprings.⁸⁰⁻⁹⁰ Other potential environmental factors that were associated with ASD include pesticides and airborne pollutants, which need further investigation.⁹¹⁻⁹⁴

Exposure Time of Environmental Factors

Environmental risk factors have been proposed to exert their effects in the development of ASD during the development of embryonic nervous system, but the development of the nervous system is a long-term process that extends from embryonic to adulthood. Some patients with ASD experience normal development after birth, but then appear stagnated and show symptoms of ASD later in development, namely degenerative ASD (regressive ASD). If the pathogenesis of degenerative ASD is different from that of other types of ASD, it would suggest apart from prenatal and early postnatal exposures, late postnatal exposure to certain environmental factors may also contribute to a subset of ASD. Therefore, surveys on postnatal environmental exposure is also essential.¹⁵

Interplay Between Genetic Susceptibility and Environmental Factors

Twin analysis and pedigree studies have demonstrated that ASDs are a group of highly inherited disease with very complex genetic predisposing factors. These may be rare mutations in single genes or a combination of multiple genetic variants. Environmental risk factors and epigenetic factors further magnified this complexity.

Hundreds of studies have been conducted to identify genes that are associated with ASD and the number of known ASD-related genetic defects has grown rapidly. Multiple well-studied genes (SNVs) and genomic regions (CNVs) have been implicated in ASD pathogenesis, such as CADPS2, CNTNAP2, FMR1, GABRB3, MECP2, NLGN3, NLGN4X, NRXN1, SHANK3, and UBE3A; 1q21.1, 2p16, 2q24, 2q37, 3p14, 5p14-15, 6p23, 7p21, 7q11.23, 10q11, 11q25, 13q14, 15q11.2-13, 15q13.3, 16p11.2, 16q22, 17p11.2, 17p12, 20p12-13, 22q11, 22q13 and Xp22 etc.⁹⁵⁻⁹⁸ But these are not enough to completely explain the pathogenesis of ASD and the recent trends of ASD prevalence. This suggests the importance of environmental factors in the pathogenesis of ASD. Epidemiological surveys found that even with the same environmental exposure, only a proportion of exposed individuals would develop ASD. Therefore, it has been speculated that whether individuals who are exposed to specific environmental conditions would develop ASD also depends on their genetic susceptibility.⁹⁹⁻¹⁰²

CONCLUSION AND OUTLOOK

In recent years, epidemiological surveys showed an upward trend of ASD prevalence, and ASD has become a common childhood developmental disorder world-wide that has brought great burden to families and societies. Currently, there is no nationwide epidemiological survey data in China, and from the end of last century to the present, epidemiological methods of the existing surveys were very limited and different from those in other countries. Therefore, epidemiological investigation of ASD in China should be improved on the basis of original data collection to obtain more effective data which can be compared with other countries. These data will help us to understand the epidemiological distribution of ASD in China, and guide rational allocation of medical resources. Epidemiology can not only help us to understand the prevalence of the disease, put forward preventive measures in the right places, but it also plays an important role in the search for possible disease etiology.

Very recently, three studies were published simultaneously from a collaborative nationwide epidemiological surveys group in China.¹⁰³⁻¹⁰⁵ The first paper described an establishment of norms for the modified Chinese version of the Autism Spectrum Rating Scale (ASRS). Participants were recruited from Shanghai, Harbin, Guangzhou and Changsha of China, and their parents and teachers completed the Chinese Parent version and the Teacher version of the ASRS.¹⁰³

The second paper further explored the psychometric properties of the modified Chinese version of ASRS. They evaluated 1,625 community-based children and 211 autism spectrum disorder (ASD) cases.¹⁰⁴

In the third paper, as a pilot study, they used Modified Chinese Autism Spectrum Rating Scales (MC-ASRS) in screening for ASD in Chinese children aged 6-12 years, through comparison with the Social Responsiveness Scale (SRS) which have been widely used for ASD screening worldwide. They recruited the

parents/caregivers of 1588 typically-developing children and 190 children with ASD aged 6-12 years to complete the MC-ASRS and SRS, and evaluated the validity of both scales in discriminating children with ASD from those developing typically. The results showed that MC-ASRS performed as well as SRS in the term of sensitivity and specificity.¹⁰⁵

These papers showed that an accuracy assessment of the Modified Chinese Autism Spectrum Rating Scale and Social Responsiveness Scale for screening ASD in Chinese Children is an important base for conduct the first nationwide epidemiological surveys in China, which should be more comparable with worldwide epidemiological surveys results reported in literature (personal communication).

China is a country with a large population, and it's estimated that there are more than one million patients with ASD in China. Although the prevalence of ASD needs to be better defined in China, emerging evidence suggests comparable rate compared to the USA. In order to prevent, precisely diagnose, and appropriately treat ASD, epidemiological investigation and study on ASD risk factors are essential. So far, studies exploring genetic/environmental risk factors of ASD were almost exclusively conducted in the Western world, which highlights the needs for further investigation under a global health framework. Given differences in environmental exposures and genetic backgrounds of China's ASD patients, future research should explore whether the same genetic and environmental risk factors that are associated with ASD in the Western world applies to that in China, and whether there are country-specific risk factors that are yet to be revealed.

Appendix: Gene resource and databases for ASD

1) AutDB (<http://autism.mindspec.org/autdb/Welcome.do>)
AutDB, cataloguing a richly annotated gene list for autism and maintained by MindSpec, has the manually curated information of different types of research data from association studies, chromosomal structural variation studies, studies of genetic disorders with single-gene mutations, and animal model studies, etc. Experts in different specialized fields are hired to extract information from published papers on autism to keep AutDB with latest up-to-date information.

Listed genes are categorized as "Genetic Association", "Syndromic", "Functional" and "Rare single gene variant". In the section of each gene, a basic summary and corresponding references are provided alongside with the information of both rare and common sequence variants, animal model existence, and protein interactions. In "Animal Model" part, construct details and phenotypic profile is available, while in "PIN" (protein interaction) part, all known linked genes are presented as a colored diagram and a detailed table as well. AutDB also contains a section of listed information of CNV research in autism and implements a helpful search query engine for further focusing based on researchers' interests.

2) SFARI Gene (<https://gene.sfari.org/autdb/Welcome.do>)
Simons Foundation received the licensed AutDB from MindSpec in 2008, and the licensed AutDB is thus named as

SFARI Gene. SFARI adds an additional interactive module which enables research community to contribute their annotations to genes. This module implements a process for gene scoring and classifies genes based on their relevance to autism into six categories of confidence level from "Highly Confidence" to "Not Supported", and another category of "Syndromic". This module encourages the participation of community researchers, and the gene score is quite intuitive for further consideration of functional studies or bioinformatic analysis. Besides this major difference, SFARI also adds other additional information. For example, in "Animal Models" section, a "Rescue Models" information is provided which mainly contains pharmaceutical intervention which helps to alleviate autism phenotypes, thus helping researchers to further examine the function of these genes in the context of development.

3) Autism Chromosome Rearrangement Database (<http://projects.tcag.ca/autism/>)

Autism Chromosome Rearrangement Database, hosted by The Centre for Applied Genomics (TCAG) of the Hospital for Sick Children, Toronto, is a database listing curated structural variants finding in autism spectrum disorder. This database contains not only extracted information from published literature but also in-house experimental data. It implements three types of information retrieval: the "Cytogenetic Data" centralized, the "Microarray Data" centralized, and the "Keyword Search" method which allows user to search for matched data of clone name, accession number, cytoband or gene symbol. The description information of individuals is provided but not in the form of tabularized data as in the case of AutDB and SFARI.

4) DECIPHER (<http://decipher.sanger.ac.uk/>)

DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans Using Ensemble Resources), maintained by Wellcome Trust Sanger Institute, is an interactive database and has a suite of tools for researchers to interpretate chromosomal structural variations. It contains chromosomal aberrations upload by more than 200 centres comprising more than 10,000 cases which are found not only in autism but in other developmental disorders as well. Users can view related information based on syndromes or karyotypes. The interface shows recorded copy number changes in color ("Loss" in red, and "Gain" in blue), while genes of recognized clinical importance are highlighted. The pathogenic contribution of the variants can be further viewed either in UCSC genome browser or ensemble browser in which the genomic and phenotypic information of each patient harboring the variants can be retrieved. The graphical presentation greatly enhances to assess clinical relevance of copy number change in users' data intuitively.

5) AutismKB (<http://autismkb.cbi.pku.edu.cn/index.php>)

AutismKB, hosted by Peking University, is an evidence-based knowledgebase for autism. It currently contains 3075 genes, 4964 copy number variations and 158 linkage regions associated with ASD based on the met of following criteria: genome-wide association studies, genome-wide CNV studies,

linkage analysis, low-scale genetic association studies, expression profiling and other low-scale gene studies, and this information can be browsed in the section of corresponding research method. Although the total numbers apparently are over-estimated and the criteria are quite loose, this database provides a "high-confidence" list of 99 syndromic autism related genes and 109 non-syndromic autism related genes based on a scoring and ranking system. AutismKB also enables user to view the result of gene set enrichment analysis by enriched GO, enriched pathway or enriched GO map, which helps to get a view of current known implicated genes in autism in the context of gene ontology.

CONFLICT OF INTEREST

None.

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