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Copy number variation and neural pathway analysis of children with autism spectrum disorder from a large Han Chinese population-based cross-sectional study

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ABSTRACT

Certain genetic events can be attributed to copy number variations (CNVs). A population in Shanghai, China was screened for autism spectrum disorder (ASD), and their CNV characteristics and possible associations with neural pathways were analyzed. A multi-stage stratified cluster sampling method was used to evaluate 3- to 12-year-old children from the general population who were in kindergarten and primary school in Shanghai. DNA samples were obtained from 133 ASD cases from preparatory ASD screening. An Affymetrix Cytoscan 750k array was used for copy number variant detection. Among the 711 children who had positive results on a survey completed by both their parents and teachers, a total of 663 (93.2%) children underwent diagnostic evaluation. Of these, 203 children were confirmed to have ASD, including 163 (80.3%) children from special education schools, 29 (14.3%) children from general kindergartens, and 11 (5.4%) children from general primary schools. Final consent had been given for blood collection, and 15 CNVs that may contribute to ASD in 133 cases were identified. The mean ages at which the ASD children with and without pathogenic CNVs (pCNVs) began to speak were 45.6 months and 29.2 months, respectively ($t = 2.452$, $P = 0.016$), and the ages of walking alone were 33.9 months and 17.5 months, respectively ($t = 5.376$, $P < 0.001$). ASD patients with pCNVs showed more abnormal facial features and signs of ASD (long faces, large noses, irregular teeth, dental caries, excessive joint extension) than those without pCNVs. The differences in tooth irregularity and dental caries between children with and without pCNVs were statistically significant ($P < 0.01$). These CNVs included a total of 993 genes. Pathway analysis was performed, and five statistically significant pathways were identified in online databases. This was the first population-based, pilot pathway analysis of CNVs in children with ASD under the diagnostic and statistical manual of mental disorders (DSM)-5 diagnostic criteria in China. Results indicate that ASD may be related to gamma-aminobutyric acid (GABA),dopamine, glycine and synaptic

Abbreviations: CNVs, copy number variations; ASD, autism spectrum disorder; aCGH, array comparative genomic hybridization; SCQ, social and communication questionnaire; IQ, intelligence quotient; EEG, electroencephalograph; MRI, magnetic resonance imaging; PEP, prolyl endopeptidase; DSM-5, diagnostic and statistical manual of mental disorders, fifth edition; GABA, gamma-amino butyric acid

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proteins. These findings are consistent with those of previous studies and provide new evidence for the role of regulation of proteolysis and endopeptidase activity in ASD.

1. Introduction

Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders that share a set of complex behavioral phenotypes involving difficulties in communication and reciprocal social interaction, stereotypic repetitive behavior, and a restricted range of interest (Huerta, Bishop, Duncan, Hus, & Lord, 2012). Increasing evidence has shown that copy number variations (CNVs) have a close association with ASD and that more genes involved in neuronal cell-adhesion or ubiquitin degradation are present in CNVs in ASD cases than in controls (Lv, Cheng, Qiu, & Zhou, 2013; Sebat et al., 2007; Tsur, Friger, & Menashe, 2016).

Genetic model and CNV studies have shown that several neuronal pathways are related to ASD, including gamma-aminobutyric acid (GABA) (Purkayastha, Malapati, Yogeeswari, & Sriram, 2015), gene of phosphate and tension homology deleted on chromosome ten (PTEN) (Lv et al., 2013), glutathione (GSH) (Bowers et al., 2011), fragile X mental retardation protein (FMRP) (Waltes et al., 2014), classic Wnt (Kalkman, 2012), and calcium and phosphatidylinositol signal pathways (Skafidas et al., 2014). There is no unified genetic pathway underlying ASD. Most of these CNV studies of ASD focused on individuals of European ancestry (Marshall et al., 2008; Pinto et al., 2014; Pinto et al., 2010). There has been a dearth of published studies of rare CNVs in Chinese autism cohorts, especially in studies of neural pathways related to ASD (Zhou et al., 2011). To address the substantial differences in terms of chromosomal location and frequency of some CNVs in the general Asian population (Park et al., 2010), the current ASD screening was conducted in a population-based sample of nearly 80,000 children in June 2014 in Shanghai, China. CNVs were detected to examine

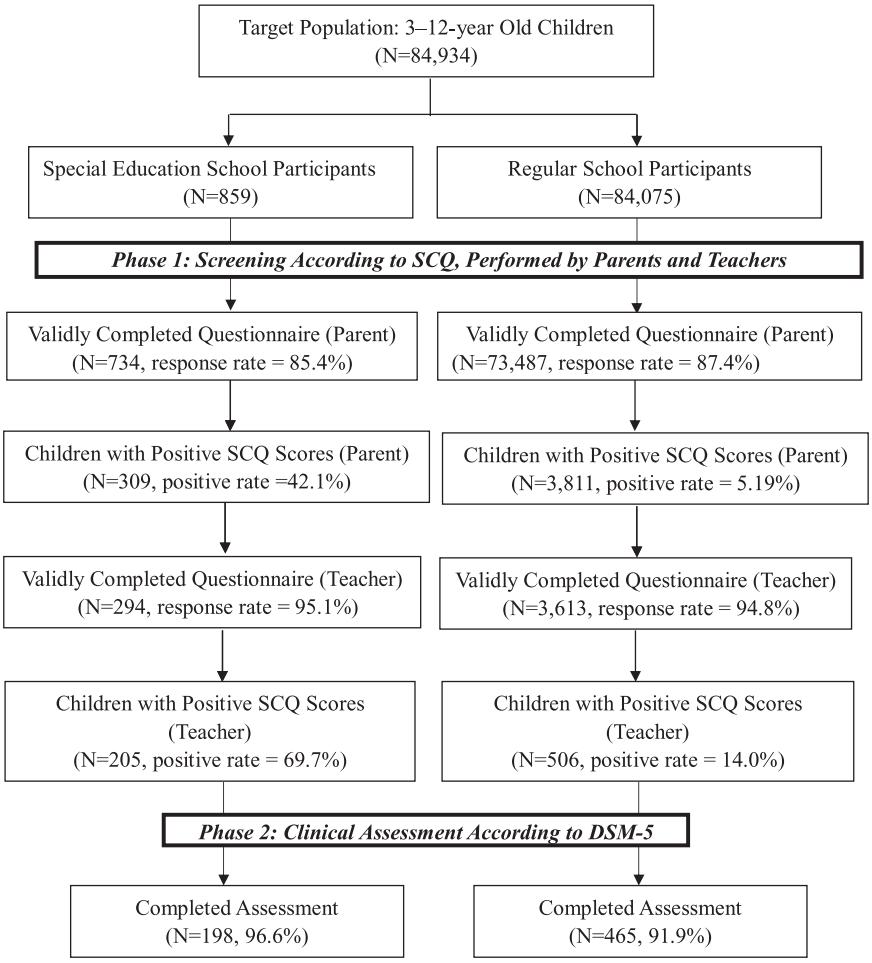

Fig. 1. Identification of Cases of Autism Spectrum Disorders in Shanghai.
Note: ASD cases were identified using a two-stage investigation. In stage 1, we systematically screened the entire sample using the Social and Communication Questionnaire (SCQ) by teachers and parents. In stage 2, children who had screened positive were further evaluated and deemed to have ASD if they met the appropriate DSM-5 criteria.