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Digit ratio (2D:4D) in a Chinese population with schizophrenia☆

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ABSTRACT

Background: Prenatal gonadal hormones may play a major role in pathogenesis of schizophrenia. It has been reported that second to fourth digit ratio (2D:4D) was influenced by the levels of exposure to prenatal testosterone and estrogen. So, 2D:4D may help to predict the disease susceptibility to schizophrenia.
Aims: The aim of this study was to investigate the relationship between the digit ratio (2D:4D) and schizophrenia in Chinese population.
Methods: We recruited 178 schizophrenics (males: 76; females: 102) and 365 controls (males: 218; females: 147) in this study. Photocopies of both hands were collected and left hand, right hand, mean hand and left minus right hand (D_{L-R}) 2D:4D were analyzed.
Results: The right and mean hand 2D:4D ratios were significantly higher in schizophrenics compared to that of controls in both males and females. The left hand 2D:4D ratio in female schizophrenics was also significantly higher than in controls. Compared to controls, the D_{L-R} 2D:4D in male schizophrenics was obviously higher. There was a weakly (but not significantly) negative correlation between the mean hand 2D:4D ratio and the age of onset.
Conclusions: The 2D:4D ratio may correlate with the schizophrenia in Chinese population, and it may be an indicator of schizophrenia.

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1. Introduction

Schizophrenia is known as a neurodevelopmental disorder. Though the origin of this disease is not well-understood, researchers have found sex differences in the age of onset, epidemiology, neural mechanisms and clinical manifestations of schizophrenia. In past decades, it has been reported that the onset of schizophrenia is correlated with perturbations in the fetal central nervous system during early development [1]. Differences in prenatal gonadal hormones have been suggested to be a reasonable explanation for the pathogenesis of schizophrenia [2]. Sex hormones, including testosterone and estrogen, are vital during brain development due to their permanent organizational effects during fetal cortical development and transient effects on neural activation after birth. In human fetuses, weeks 8–24 of gestation are an extraordinarily sensitive period due to permanent organizational events occurring in the developing cortex; at this time, there is also a peak in testosterone levels [3]. After birth, gonadal hormones can alternatively enhance neural changes later in life [4]. In Arnold's report [5], gonadal androgen, especially testosterone, played a crucial role in modulating nerve cell migration, synaptogenesis and dendritification. Further researches have demonstrated that the altered laterality in schizophrenia was due to disrupted prenatal testosterone (PT) [6] or absence of the protective effects of prenatal estrogen (PE) [7]. Several reports have suggested that schizophrenics, particularly males, have reduced strength of hand preference [8], lessened left hemisphere capacity and decreased representation of language [9], which are all consistent with altered prenatal gonadal hormone levels and altered laterality in schizophrenia. Although controversial, it has been hypothesized that unbalanced exposure to sex steroids is related to numerous diseases in adulthood, such as some cancers, fertility, heart disease and schizophrenia [10–14].

In recent years, digit ratios, especially the ratio of second finger length to fourth finger length (2D:4D), have received considerable attention as new anatomical indicators that can reflect the level of exposure to PT and PE. Manning and colleagues [15] have suggested that digit ratios are developed early in pregnancy and are maintained in later fetal periods and after birth and that digit ratios may indicate variations in circulating prenatal gonadal hormones, with lower 2D:4D representing relatively higher PT and lower PE. Subsequently, some authors have reported similar results to Manning's. Furthermore, several lines of evidence, especially recent evidence from a mouse model, suggest that prenatal hormone exposure or sensitivity to testosterone and

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estrogen influenced the 2D:4D ratio, with a higher ratio of testosterone relative to estrogen correlated with a lower 2D:4D ratio [16].

To date, there have been a number of studies investigating the relationship between 2D:4D ratio and central nervous system diseases, including autism, schizophrenia, and others; however, not all of the results are consistent. Manning et al. [17] reported that the 2D:4D ratio was significantly lower in children with autism or autism spectrum disorders compared to matched control children. Later, the investigation conducted by Arato et al. [18] revealed that schizophrenics had a more "feminine" phenotype, with higher relative length of 2D compared to 4D in both males and females. Walder et al. [19] investigated the 2D:4D ratio in Caucasian adolescents with schizotypal personality disorder and found that male patients had higher 2D:4D ratio than the controls. On the contrary, Daly et al. [20] found no effect in a non-clinical population considered at high risk for schizophrenia. Gooding et al. [21] indicated that neither negative schizotypy nor positive schizotypy was associated with altered digit ratio. Venkatasubramanian et al. [22] found that female schizophrenia patients had lower 2D:4D ratios than controls but reported no difference in males. Recently, Collinson et al. [14] studied the digit ratio of schizophrenic inpatients and outpatients compared with controls and observed higher 2D:4D ratios in male schizophrenics.

We conducted an investigation of the 2D:4D ratio in schizophrenia patients from the Ningxia region, China to determine whether 2D:4D ratio could be regarded as an indicator to identify schizophrenia during early development.

2. Subjects and methods

2.1. Study site and subjects

In our study, we collected 76 male (age: 17–59 years, mean age ± S.D. = 32.50 ± 10.62) and 102 female schizophrenia patients (age: 15–62 years, mean age ± S.D. = 34.80 ± 10.05) during 2014 to 2015. At the same time, we recruited 218 males (age: 17–60 years, mean age ± S.D. = 32.05 ± 8.40) and 147 females (age: 17–63 years, mean age ± S.D. = 36.10 ± 10.38) as the control groups. All the participants were from Yinchuan city, the Ningxia region, China. The controls were exhibited healthy physical and mental states. The patients were all diagnosed with schizophrenia in term of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [23]. The subjects with finger fractures or abnormal defects were excluded.

2.2. Ethical statements

This study was approved by the Ningxia Medical University Committee for the Protection of Human Subjects, and all the participants had informed written consent before the experiment.

2.3. Measurement of digit ratios

All subjects had their left and right hand palms photographed with keeping the camera perpendicular to the palms side in the same height. When taking photos, the participants were required to spread their fingers and hand palms. The Adobe Photoshop Software was used to analyze the photos. Index finger and ring finger of both hands were measured twice from the tip of the finger towards the middle point of the most proximal crease to the palm to get more exact measurement [24]. Then we calculated the ratios of digit lengths between index finger and ring finger, and regarded the average digit ratio value of two measurements as the final result of each indicator. In addition, the mean hand 2D:4D ratio showed the average value of left hand 2D:4D and right hand 2D:4D, the left minus right hand 2D:4D ($D_{L\text{-}R}$ 2D:4D) was calculated based on the formula: the $D_{L\text{-}R}$ 2D:4D = left hand 2D:4D - right hand 2D:4D.

2.4. Statistical analysis

Data analysis were conducted with SPSS 19.0 software and expressed as mean ± standard deviation (S.D.). Comparison of the variables between groups was carried out by using independent sample *t*-test. The Pearson correlation coefficient test was done to discover the correlation between 2D:4D digit ratios and age of onset in schizophrenia. The *p*-value < 0.05 was regarded as having a significant difference.

3. Results

3.1. Mean values and distribution of 2D:4D ratio

There was no significant difference between each individual's first and second measurements of each digit length ($p > 0.05$).

In both males and females, no significant difference was found in 2D:4D ratio between the right and left hands neither in controls nor in schizophrenic patients respectively ($p > 0.05$). The range of 2D:4D ratio for controls was similar to the patients (Tables 1–2).

No significant sex difference was found in 2D:4D ratio among the control subjects ($p > 0.05$).

The patients have significantly higher 2D:4D ratios in the right and mean hands compared to that of controls in both males (right hand: $t = -4.11$, $p = 0.000$; mean hand: $t = -3.29$, $p = 0.001$) (Table 1) and females (right hand: $t = -3.59$, $p = 0.000$; mean hand: $t = -4.92$, $p = 0.000$) (Table 2). In males, there was no significant difference in left hand 2D:4D ratio between two groups ($t = -1.52$, $p = 0.13$) (Table 1); while in females, the patients had significantly higher left hand 2D:4D ratios than controls ($t = -4.74$, $p = 0.000$) (Table 2). About the $D_{L\text{-}R}$ 2D:4D, there was a significantly difference between two groups in males ($t = 2.39$, $p = 0.02$) (Table 1), but not in females ($t = -0.43$, $p = 0.67$) (Table 2).

3.2. Correlations between age/age of onset and 2D:4D ratio in controls and patients

In Table 3, it showed the correlation between the age of onset in schizophrenics (present age in controls) and 2D:4D digit ratios respectively. We did not found any significant correlation between age (in controls) or age of onset (in patients) and 2D:4D ratio both in males and females (all $p > 0.05$). However, there was a weakly negative correlation trend between the age of onset and the mean hand 2D:4D in male schizophrenics ($r = -0.211$, $p = 0.067$) (Fig. 1).

Table 1
Mean values and ranges of 2D:4D ratio in both patients and controls in males.

	Controls (N = 218)		Schizophrenics (N = 76)	
	Mean (S.D.)	Range	Mean (S.D.)	Range
Left hand 2D:4D	0.950 (0.035)	0.837–1.057	0.957 (0.034)	0.895–1.064
Right hand 2D:4D	0.948 (0.037)	0.812–1.045	0.968 (0.037)**	0.876–1.076
Mean hand 2D:4D	0.949 (0.032)	0.843–1.033	0.963 (0.028)**	0.909–1.033
$D_{L\text{-}R}$ 2D:4D	0.002 (0.032)	−0.070–0.109	−0.011 (0.044)*	−0.127–0.113

* $p < 0.05$ (difference of 2D:4D between controls and schizophrenics).
** $p < 0.01$ (difference of 2D:4D between controls and schizophrenics).

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