The Ratio of 2nd to 4th Digit Length in Korean Alcohol-dependent Patients

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Objective: The ratio of 2nd to 4th digit length (2D:4D) is a sexually dimorphic trait. Men have a relatively shorter second digit than fourth digit. This ratio is thought to be influenced by higher prenatal testosterone level or greater sensitivity to androgen. The purpose of this study is to investigate the relationship between alcohol dependence and 2D:4D in a Korean sample and whether 2D:4D can be a biologic marker in alcohol dependence.

Methods: In this study, we recruited 87 male patients with alcohol dependence from the alcohol center of one psychiatric hospital and 52 healthy male volunteers who were all employees in the same hospital as controls. We captured images of the right and left hands of patients and controls using a scanner and extracted data with a graphics program. We measured the 2D:4D of each hand and compared the alcohol dependence group with the control group. We analyzed these ratios using an independent-samples *t*-test.

Results: The mean 2D:4D of patients was 0.934 (right hand) and 0.942 (left hand), while the mean 2D:4D of controls was 0.956 (right hand) and 0.958 (left hand). Values for both hands were significantly lower for patients than controls ($p<0.001$, right hand; $p=0.004$, left hand).

Conclusion: Patients who are alcohol dependent have a significantly lower 2D:4D than controls, similar to the results of previous studies, which suggest that a higher prenatal testosterone level in the gonadal period is related to alcoholism. Furthermore, 2D:4D is a possible predictive marker of alcohol dependence.

KEY WORDS: Alcohol dependence; Finger length; Biological markers; Genetic epigenesis.

INTRODUCTION

Alcohol use disorder is common addictive condition, with the prevalence of alcohol dependence reaching approximately 9.7% in the United States and 7.1% in Korea.[1]

Alcohol use disorders is diagnosed by the need for daily consumption of alcohol, consumption of large amounts of alcohol and inadequate daily function.[2] Alcohol dependence is related to impulsiveness, sensation seeking and extraversion.[3] Alcohol dependence is a complex disorder

attributed to the interaction of genetic and environmental factors and it is difficult to identify the disease predisposition of alcohol dependence. Men are much more likely than women to become binge or heavy drinkers.[4]

There have been many efforts by researchers to establish biologic markers of alcoholism. Biochemical traits such as monoamine oxidase and adenylyl cyclase are associated with alcohol dependence.[5,6] A neuroimaging-derived endophenotype developed with functional magnetic resonance imaging has been confirmed to react to alcohol cues.[7] Genetic variation in aldehyde dehydrogenase type 2 that changes alcohol to metabolize can also influence susceptibility to alcohol dependence.[8] The P300 component of event-related potential is another possible biologic marker of alcoholism.[9]

In recent years, the relative length difference between the 2nd digit (index finger) and 4th digit (ring finger) has been the focus of many psychiatric investigations. Many studies have suggested the association of psychological traits to the ratio of 2nd to 4th digit length (2D:4D), and

there have been various attempts to associate psychiatric diseases with 2D:4D.

2D:4D is a sexually dimorphic trait.[10,11] In the human hand, men have a relatively shorter 2nd finger than 4th finger, while women have 2nd and 4th digits of equal lengths or a longer 2nd finger. Therefore, 2D:4D in men is usually lower than it is in women.[12] This dimorphic tendency is typically clearer in the right hand than in the left.[13-15]

Differences in 2D:4D are associated with prenatal testosterone and estrogen. In previous studies, 2D:4D was thought to be influenced by higher prenatal testosterone level or greater sensitivity to androgen.[13,16] In the early gestational period, the fetus is exposed to fetal testosterone and 2D:4D is thought to be fixed early in development.[17]

Low 2D:4D has been correlated with masculine traits in men and women.[18,19] Nonheterosexual males have been observed to have high 2D:4D, and nonheterosexual females have been reported to have low 2D:4D.[15] Aggression and sensation seeking personality traits are correlated with 2D:4D. Low 2D:4D, representing the masculine/ high androgen type, is correlated with higher levels of aggression and sensation seeking[20] as well as with physical aggression in men.[21] A natural affinity for sports such as football is also associated with 2D:4D.[22] In addition, attention deficit hyperactivity disorder symptoms and 2D:4D are correlated.[23] Some studies have investigated the relationship between schizophrenia and 2D:4D.[24]

Recently a study suggested that 2D:4D is lower in alcohol-dependent patients than it is in normal controls.[25] Alcohol-dependent patients in a German hospital were compared with normal controls, and the result showed that alcoholics have lower 2D:4D.

The object of this study is to compare the finger length of alcohol-dependent patients and normal controls. There have been few studies of alcohol dependence and 2D:4D, therefore we seek to confirm the relationship between alcoholism and 2D:4D as a function of gonadal testosterone level. And we investigate whether 2D:4D can be a biologic marker in alcohol dependence. This study is the first to research the relationship of 2D:4D and alcoholism in Korea. Although 2D:4D did not vary by ethnicity in a previous study,[12,26] we aim to confirm the relationship of 2D:4D and alcohol dependence in Korean.

METHODS

Subjects

We measured 2D:4D in the right and left hands of 87 male inpatients from the alcohol treatment center of Keyo Psychiatric Hospital, Korea. All participants were diagnosed with alcohol dependence by a clinician using the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria. Patients also underwent the Alcoholism Screening Test of the National Seoul Mental Hospital-I (NSAT-I),[27] and were scored using the Korean version of the alcohol dependence scale (ADS-K), which is a clinical measure of alcohol dependence.[28]

The controls were 52 male volunteers who were composed of alcohol-related facilities who had no history of psychiatric illness. The control group was evaluated with the NSAT-I to rule out alcohol problem.

Ethics approval was obtained from Yong In Psychiatric Institute. All participants provided informed consent.

Measurements

Demographic variables, including age, age of first alcohol consumption, years of drinking, average daily amount of drinking (measured in bottles of Soju, the name of a distilled beverage native to Korea, 20% to 25% ethanol, 375 ml), were investigated among the alcohol-dependent subjects.

We used a scanning technique because the scanned image is fixed, less subjective and is possible to blind test. We employed the Canon Pixma MP 258 scanner (Canon Corporation, Tokyo, Japan) to capture the hand images. After scanning, we obtained the questionnaire scores. Participants were required to put both hands palm down on the window of the scanner and spread all fingers. Scanning was conducted by one researcher.

The images were analyzed using Photoshop 7.0.1 (Adobe Systems, San Jose, CA, USA). The original pictures were magnified ×2 for accuracy. The proximal point was the middle of the basal crease on the 2nd and 4th finger. The distal point was the tip of the finger. Two points were measured by "pen tool" in Photoshop program. This process was performed by three experimenters who were blinded to group enrollment status. The mean of the three measurements was used for analysis.

Statistical Analysis

To identify any association between demographic variables and 2D:4D of each hand, correlation analysis was performed. We compared 2D:4D of each hand of the alcohol-dependent and control groups. We analyzed these ratios using an independent-samples t-test. Statistical analysis was performed with IBM SPSS Statistics software ver. 20.0 for Windows (IBM Co., Armonk, NY, USA). The significance levels of all analyzed data were verified with-

in a range of $p < 0.01$.

RESULTS

Inter-rater reliability of the three measurements was high. Intraclass correlation coefficient (ICC) of the right 2nd digit was 0.819 and ICC of the right 4th digit was 0.889. In left hand, ICC of the 2nd digit was 0.963 and the 4th digit was 0.864.

The mean age of controls was 48.32. Demographic variables are presented in Table 1. There was no correlation between demographic variables and 2D:4D.

The mean 2D:4D of alcohol-dependent patients was 0.934 (right hand) and 0.942 (left hand), while that of controls was 0.956 (right hand) and 0.958 (left hand). 2D:4D

**Table 1.** Demographic and clinical characteristics of alcohol-dependent patients (n=87)

Variable	Data
Age (yr)	51.2±10.2
Total score of ADS-K	20.5±10.7
Age of first alcohol consumption (yr)	20.2±5.4
Years of drinking	27.2±12.2
Average daily consumption (bottles of Soju)	4.14±1.80

Values are presented as mean±standard deviation.
ADS-K, Korean version of alcohol dependence scale.
Soju, the name of a distilled beverage native to Korea.

of patients was significantly lower than that of controls in both the right ($p < 0.001$) and left ($p=0.004$) hands (Table 2). Figures 1 and 2 demonstrate these differences.

DISCUSSION

We examined the relationship between 2D:4D and alcohol dependence in a Korean sample. We suspect that prenatal testosterone influences 2D:4D and that alcohol-dependent patient may have been exposed to higher prenatal testosterone.

In our study, alcohol-dependent patients had lower 2D:4D than controls. This was similar to the results of a previous study.[25] Through these two studies, the relationship between 2D:4D and alcoholism has been clarified. Therefore, we propose the potential of 2D:4D as a biologic marker of alcoholism. Digit ratios are known to be fixed by the age of 2 years.[12,13,22,26,29] Alcohol use disorders was more frequent in men than in women.[1] In previous study, alcohol dependent patients showed impulsiveness, sensation seeking and extraversion.[3] Therefore, low 2D:4D of alcohol-dependent patients could reflect the masculine trait of the alcoholism. But we could not find any relationship between the clinical characteristics and 2D:4D in previous study. Further studies should compare various clinical features and 2D:4D in alcohol-dependents

Table 2. Differences in 2D:4D between alcohol-dependent patients and controls

	Patients (n=87)	Control (n=52)	t	p
2D:4D right hand	0.934±0.026	0.956±0.031	−4.665**	<0.001
2D:4D left hand	0.942±0.027	0.958±0.029	−2.909*	0.004

Values are presented as mean±standard deviation.
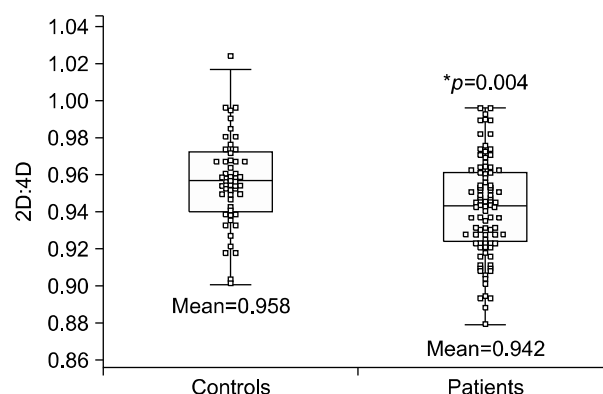2D:4D: the ratio of 2nd to 4th digit length.
*$p < 0.01$, **$p < 0.001$.
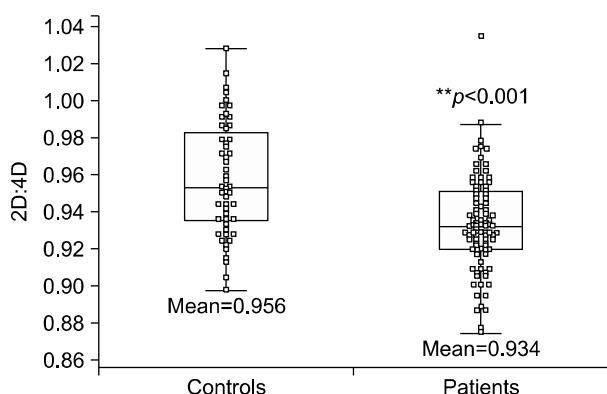
Fig. 1. The ratio of 2nd to 4th digit length (2D:4D) in right hands between controls and alcohol-dependent patients.

Fig. 2. The ratio of 2nd to 4th digit length (2D:4D) in left hands between controls and alcohol-dependent patients.

patients.

In many psychiatric diseases, the prevalence, severity and course of illness are sexually dimorphic.[30] Molecular genetic findings confirm the sexual dimorphism of many diseases. For example, autism is related to a male-specific linkage peak at chromosome 17q11.[31] Sexual hormones, such as testosterone and estrogen, play a key role in generating the phenotypical and physiological differences between the sexes. Alzheimer's disease symptoms in postmenopausal women are decreased by estrogen replacement therapy.[32] Sexual dimorphism may be influenced by sex hormone mediation in the epigenetic regulation of genes.[30]

Low 2D:4D and low number of trinucleotide (CAG) repeats are related to high activation of androgen-responsive genes.[33] Therefore, 2D:4D is a sexual dimorphic trait caused by androgen and estrogen regulation.

Further experimental study recently investigated differences in finger length and revealed that the 2nd digit had higher androgen receptor and estrogen receptor-α activity than the 4th digit in a mouse model.[34] The results suggested that multiple regulatory factors including gene expression, sexual hormone receptor distribution and modulation of androgen and estrogen signaling are related to finger length.

The results of our study varied from those of a previous study by Kornhuber et al.[25] Our study showed that the 2D:4D of controls was 0.956 (mean) in the right hand. However, in the previous study, the 2D:4D of controls was approximately 0.976 in the right hand. This variation of the values of 2D:4D may be related to ethnic, methodological or enrollment differences.

There have been few non-Caucasian studies on 2D:4D. In the study for schizophrenia in Asian groups, 2D:4D of the control group was 0.957 (mean) in men.[24] Another study on 2D:4D and schizophrenia in Korean men found the 2D:4D of the control group to be 0.953 (mean).[35] The results of these studies for Asian groups are similar to those of our study. Nevertheless the ethnics, 2D:4D is known to be adaptive. The numerical values may vary among races. Future studies should take this into consideration.

Thus far, many studies on digit ratios were conducted with varying methodology. Digit length has been measured both directly and indirectly by duplicator and scanner. Most researchers used Vernier calipers for direct measurement, which have a tolerance range of 0.01 mm. This has some benefits, such as that the experimenter can see the point of the finger tip and basal crease. The lack of blinded

investigation and subjective intervention are crucial limitations of this technique, however. A duplicator also can be used, but the tip and basal crease of the duplicated finger are sometimes ambiguous, although the image sheets can be well kept. Scanning can be affected by the type, performance and resolution of the equipment and imaging programs used. This method can save the image, revive the results and allow for blinded studies. These methodological differences can cause variation in absolute values.

The first limitation of our study was that we only included male patients. The previous study by Kornhuber et al.[25] included both sexes, but the strength of the correlation was weaker in females than in males.[25] Some studies have found that alcohol drinking among women is related to masculinity.[36] Therefore, we conjecture that it is possible that female alcoholics also have low 2D:4D.

Second, 2D:4D might be suggested to present the influence of sex hormones, but it is not a direct method to reflex to sex hormones. In previous study, the prevalence of alcohol use disorders showed that men are more three times than women.[1] And the concentration of testosterone in alcohol dependence was higher than that in control group.[37] Therefore sex hormone, especially testosterone, could relate to develop the alcohol dependence. But further studies are needed to consider additional methods to compare the direct measurement and 2D:4D among alcohol-dependent patients.

In conclusion, alcohol-dependent patients have lower 2D:4D, suggesting that that higher prenatal testosterone levels in the gonadal period are related to alcoholism. 2D:4D is a potential biologic marker of alcohol dependence.

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