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# The ratio of 2<sup>nd</sup> and 4<sup>th</sup> digit length: a biomarker for methamphetamine dependence?

## Abstract

**Objectives:** The ratio of 2<sup>nd</sup> and 4<sup>th</sup> digit length (2D:4D) is considered to be a sexually dimorphic trait. Low 2D:4D is implicated in alcohol dependence and heroin dependence and correlated with psychological traits such as aggression, physical aggression, and sensation. The purpose of this study is to compare the 2D:4D between methamphetamine (METH) dependence and controls and the 2D:4D ratio that is a potential biomarker for METH dependence.

**Methods:** In this study, 40 patients diagnosed with METH dependence in Eulji University Gangnam Eulji Hospital and 50 healthy volunteers were all employees in the same hospital. Images of participants' hands were created using a scanning device. The images contained both the right and left hands; computer software was used to measure the 2D:4D ratio for both hands. We compared the ratios, analyzed by t-test, between the METH dependence group and the control group.

**Result:** The mean 2D:4D values were 0.941 (right hand) and 0.943 (left hand) for the patients with METH dependence; in contrast, they were 0.961 (right hand) and 0.961 (left hand) for the control group. These values were significantly smaller than the control in patients' right hands ( $p=0.003$ ) and left hands ( $p=0.012$ ).

**Conclusion:** Patients with METH dependence had smaller 2D:4D ratios than those in the control group, which is similar to the results from the previous substance use disorder studies. Thus, elevated prenatal testosterone levels during the gonadal period could be related to future METH problems. Furthermore, the 2D:4D ratio is a potential marker for the prediction of METH dependence.

KEY WORDS: Methamphetamine dependence; Finger length; Biomarkers; Genetic epigenesis.

## Introduction

Methamphetamine (METH) is a psychostimulant drug acting on the central nervous system (CNS) and a highly addictive substance. METH is the cause of various worldwide addiction problems in medical, socioeconomic, and legal domains.<sup>1)</sup>

METH is a neurotoxic substance, so that METH dependence can cause various neurodegenerative problems affecting cognitive functions.<sup>2,3)</sup> Additionally, psychiatric problems, such as psychosis, depression, and anxiety, commonly occur in METH addiction.<sup>4)</sup>

Dopamine is known to be the neurotransmitter playing a central role in the development of addictive disorders. The dorsal striatal dopamine pathway is known to play a significant role in METH addiction.<sup>5)</sup> Additionally, genetics significantly influence the manifestation of most addictive disorders. In alcohol dependency, which could be the most common form of substance abuse, the heritability is approximately 40%, and the concordance rate for male identical twins is approximately 0.59.<sup>6,7)</sup>

METH dependence is likely a disorder with multiple genes involved. The concordance rates were estimated to be between 0.33 to 0.44 for male identical twins and 0.79 for female identical twins.<sup>8,9)</sup> These results indicate a high heritability of METH dependence.

Previous research investigated the role of prenatal testosterone in the development of addictive disorders. Prenatal testosterone is known to be associated with the development of aggression, impulsivity, and sensation-seeking tendencies. In addition, the prenatal testosterone level of amniotic fluid is associated with the development of

masculine characteristics in a fetus.<sup>10,11)</sup> The aggression, impulsivity, and sensation-seeking tendencies commonly occur in patients with addiction problems, so that prenatal testosterone could play a crucial role in the development of addiction.<sup>12)</sup> Thus, fetal exposure to sex hormones is likely to be significantly implicated in the development mechanisms of substance addiction, including METH, alcohol, and heroin.<sup>13)</sup>

Among genes affecting fetal exposure to sex hormone, the hox family genes exert modulating influences on the development of sex organs.<sup>14)</sup> Sex hormones such as estradiol, progesterone, and testosterone are regulated by hox gene expression. Notably, the ratio of 2<sup>nd</sup> and 4<sup>th</sup> digit length(2D:4D) was found to be affected by the exposure to sex hormones via such genes.<sup>15)</sup>

The 2D:4D is a known sexual dimorphic trait and is lower in men than in women.<sup>16)</sup> The 2D:4D ratio is affected by fetal exposure to sex hormones. The ratio is determined at about 14 weeks in gestation, fixed at about two years of age, and is not altered by other factors, including environmental factors.<sup>17,18)</sup> The 2D:4D ratio is negatively correlated with prenatal testosterone for both men and women; it could be an indirect index of intrauterine testosterone exposure. Over-exposure to testosterone or increased sensitivity of male hormone receptors can lead to a relatively long 4<sup>th</sup> finger, decreasing the 2D:4D ratio.<sup>16,19,20)</sup> The mechanism of length adjustment of the 4<sup>th</sup> finger by intrauterine sex hormones is due to the different activities between androgen receptors and estrogen receptors in the second and fourth fingers.<sup>21)</sup> The inactivation of androgen receptors hinders the growth of the fourth finger, increasing the 2D:4D ratio. In contrast, the inactivation of estrogen receptors promotes the growth of the 4<sup>th</sup> finger, decreasing the 2D:4D ratio. Additionally, administering androgen promotes the

development of the 4<sup>th</sup> finger, decreasing the 2D:4D ratio.

Previous studies showed a different level of masculinity **or** femininity depending on the degree of intrauterine exposure to sex hormones in men with the same sex chromosome and sex-determination system.<sup>22)</sup> Additionally, a low 2D:4D ratio is associated with masculine traits such as aggressiveness, extroversion, and adventurousness, while a high 2D:4D ratio is associated with increased fear of uncertainties.<sup>23-25)</sup>

In previous studies about the relationship between the 2D:4D ratio and addictive disorders, the 2D:4D ratio was lower in an alcohol dependence group than in a normal control group.<sup>13,26)</sup> This result could be because prenatal exposure to sex hormones influenced the development of the addiction in patients with alcohol dependence. Alcohol dependence is more prevalent in men than in women.<sup>27)</sup> Because patients with alcohol dependence are characterized as having masculine traits such as impulsivity and aggressiveness, the findings from the previous studies may indicate that the temperament formed due to the actions of intrauterine sex hormones during the developmental phase should be related to the manifestation of alcohol dependence. Additionally, the 2D:4D ratio was seen to be lower for the addiction group of another substance (e.g., heroin) than the normal group.<sup>28)</sup> In that study, heroin addiction was related to relatively high degrees of aggressiveness and impulsivity, similarly to the case with the patients who have other types of substance addiction, where the 2D:4D ratio is correlated.

Therefore, recent studies argue that the 2D:4D ratio is an essential biomarker for indirectly confirming intrauterine sex hormone exposure in addictive disorders.

This study aims to compare the lengths of the digits between the patients with METH addiction and the normal group. Previous studies have measured the 2D:4D ratio in patients addicted to several substances and compared the measurement with the normal group, but many forms of substance addiction have not yet been studied in this manner. Notably, METH is an addictive substance that causes serious problems worldwide by damaging nerve cells and tissues in the human brain, leaving severe sequelae behind in the patients with addiction. Thus, it is crucial to identify the pathophysiological mechanisms related to the development of METH dependence. This study proposes that the 2D:4D ratio is a potential biomarker for METH dependence.

## Methods

### Participant

We measured the lengths of the second and fourth fingers in a total of 40 patients undergoing treatment at the outpatient department of the Gangnam-Eulji Hospital. The patients who participated in this study were diagnosed with METH dependence by a psychiatrist according to the DSM-IV diagnostic criteria. Participant's ages ranged from 23 to 63 years old, and those who had other accompanying addictive disorders were excluded from the study. The normal control group consisted of 50 male volunteers who were in the hospital facility and had no recorded history of a psychiatric illness. The control group was checked by the alcohol screening test of national Seoul mental hospital (NAST).<sup>29)</sup> NAST is the screening questionnaire designed for alcohol use disorder. It consists of 12 items to screen alcoholics. The control group who had 4 NASTI score and more were excluded in the experiment. The demographic information of the study participants is presented in Table 1. All participants signed the consent form and volunteered to participate in the study after receiving the explanations from a researcher about our study's goal.

All procedures were carried out with the approval of institutional review board of the Eulji University of Korea (EUIRB2018-122)

### 2. Measurement

There are various ways to measure the 2D:4D ratio according to the previous studies. This study employed a scanner system used by McFadden et al. for scanning to create

the images of participants' hands that were edited using image editing software to store the finger images and image analysis.<sup>30)</sup> In our study, the scanner used was the Canon MP 258. A psychiatrist performed the procedure. Participants were instructed to place both of their hands on the scanner's glass plane comfortably with the palm facing down. The obtained images were analyzed using Photoshop 7.0.1 image-editing software. The reference point in the image was the mid-point between the tip and the basal crease of a finger and assisted the measurement of the fingers. The original image was magnified two-fold to increase the accuracy of the measurement. The original length could be measured accurately using the software despite the magnification of images. A feature named the "pen device" was used to measure the second decimal's accuracy of 0.01 mm. Two psychiatrists and one clinical psychologist performed the length measurement, and they did not participate in the rest of the experiment. The average measurement values were used for analysis.

### 3. Statistical analysis

Independent samples t-test was used to verify the group differences in terms of age, age at first drug use, the period of drug use, and the 2D:4D ratio. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), v18.0, the Windows version, and statistical significance were set at  $p < 0.05$ .



## Results

We exhibited demographic variables, table 1. There were no correlation between demographic variables and 2D:4D of the patients.

The mean 2D:4D of patients was 0.941(Rt hand), 0.943(Lt hand). Control was 0.961(Rt hand), 0.961(Lt hand). In Rt hand, Patients` was significantly lower than controls`( $p=0.003$ ) and also in Lt hand, patients` was significantly lower than controls`( $p=0.012$ )(see table 2). In figure 1 and 2, we showed Rt and Lt 2D:4D between normal controls and METH dependence patients.

## Discussion

This is the first study investigating the validity of the 2D:4D ratio as an indirect measure of intrauterine testosterone in METH addiction. We examined the relationship between the 2D:4D ratio and METH addiction. We assumed that prenatal testosterone exposure influenced the 2D:4D ratio; patients with METH addiction may have been exposed to a higher level of prenatal testosterone exposure; thus, the 2D:4D ratio was hypothesized to be lower in the METH addiction group than in the normal control group.

The 2D:4D ratio was significantly different in both the right hand and the left hand, but the difference was more significant in the right hand, consistent with the previous study results.<sup>31)</sup>

Our study is meaningful because we verified the crucial role of sex hormones in developing METH dependence by confirming a lower 2D:4D ratio in the METH patient group than in the normal group. Our result is consistent with the previous studies regarding the patients with alcohol and heroin substance dependence; thus, it can be interpreted as intrauterine sex hormone affecting substance addiction problems.

The intrauterine exposure to sex hormone is related not only to the 2D:4D ratio but also to fetal brain structures and various physiological functions.<sup>32)</sup> Specifically, testosterone plays a role in the formation of the mesolimbic reward system (MRS) that is involved in addictive behaviors. The MRS is implicated in the brain's dopamine pathway and is closely associated with impulsive and addictive tendencies and aggressive behaviors. Additionally, it has been reported associated with personality traits such as novelty-seeking or reward dependence behaviors related to the brain areas like the

substantia nigra and ventral tegmental area.<sup>33)</sup> A different study reported that the ventral striatal and midbrain region is involved in impulsive behaviors, like attempting to use drugs, in adolescents with a higher tendency for novelty-seeking.

The personality traits in patients with substance addiction are characterized by impulsivity and novel-seeking.<sup>34)</sup> Additionally, a previous study has reported that the novelty-seeking properties in patients with METH dependence were related to the genes associated with dopamine receptors.<sup>35)</sup> Impulsivity is known to be higher in patients with alcohol dependence, and childhood development affects impulsivity.<sup>36)</sup> Patients with heroin addiction have also shown higher impulsivity than the normal control groups.<sup>28,37)</sup> These studies argued that these impulsive tendencies should be related to the anterior cingulate cortex (ACC) in the brain and prefrontal cortex (PFC) dysfunctions.

Like the patients with addiction to other substances, patients with METH dependence are highly impulsive and share the general characteristics associated with the addictive behaviors. Thus, such tendencies and the brain's structural characteristics seem to play a crucial role in substance addiction development.

To summarize, the 2D:4D ratio for patients with METH dependence is affected by intrauterine exposure to sex hormone; thus, intrauterine sex hormone should reflect the patient's temperament. We believe that the 2D:4D ratio is a meaningful biomarker for the development of METH dependence.

The limitations of our study are as follows. First, our study participated in only the male patients. Although METH addiction can develop in both men and women, we could not recruit female patients with METH dependence. In Korea, METH addiction also

affects men and women alike. Additionally, the physiological and psychological differences between men and women with METH dependence are unclear. Thus, investigating the causative factors of METH addiction relating to the intrauterine sex hormone exposure and the gender difference in developing METH dependence would be meaningful.

Next, this study did not clarify the different uses of the substance by participants. The drug use by patients with METH dependence can be characterized in various ways, including the age of developing drug dependence, the period of drug use, and the aspects of the drug. For this reason, patients with METH dependence may develop characteristics of a different temperament. For example, in alcohol dependence, how alcohol is used can differently define the clinical subtypes. Cloninger et al. used genetic predisposition to divide alcohol dependence's clinical subtypes: Type I and Type II.<sup>38)</sup> The subtype II of alcohol dependence is characterized to develop at a relatively young age, <25 years old, and occurs in men primarily. They often lose self-control against drinking, frequently drink excessively, have decreased desire for avoiding injuries, and often have a history of antisocial tendencies. They tend to drink for pleasure and show an inadequate response to treatment.<sup>39)</sup> Personality-wise, they seek sensory experiences, are characterized as an extrovert, are less affected by childhood environment, and tend to have alcoholic fathers. In contrast, subtype I of alcohol dependence have a higher desire to avoid injuries and drink alone. They develop dependence at an older age, >25 years, affected by childhood family environment, and show the same incidence rate in men and women. Studies exist showing different clinical and biological characteristics depending on the subtypes of alcohol dependence, for example, a study about the existence of

abnormal activation of platelet monoamine oxidase only in the subtype II.<sup>40)</sup> Similarly, the patients with METH dependence's clinical characteristics vary too much to be considered a disease of homogeneous characteristics; thus, patients with METH dependence could also be categorized according to specific criteria. However, there have not been many studies about the METH dependence patients' clinical categories based on their temperament and biological properties. Future studies are encouraged on this topic, which may help to elucidate the etiology of METH addiction further.

Another limitation is that there has been no methodological standardization yet. Researchers have used various ways to measure the 2D:4D ratio. Previous studies used tools like vernier calipers to measure the length direct.<sup>41)</sup> This method is advantageous since one can visually examine the fingers while measuring the length. Vernier calipers can measure with 0.01 mm precision. However, a researcher has not been blinded to which group the participant belongs. Thus, there is room for researcher bias. Besides, the measurement result may not be preserved, and an error may occur depending on the measurement conditions. Recent studies use indirect measurement methods. A copy machine can be used to make a printed copy of the palm, or a scanner can be used to scan the image of fingers for measurement.<sup>13</sup> Such methods are advantageous because blindness is maintained during measurement, and the resulting images can be conveniently stored. The method should still be standardized in terms of the scanner specifications, types, performance, and image editing software use. This study assessed the 2D:4D ratio using a scanner and image editing software to increase the objectiveness and preservation of the measurements. One researcher scanned all the finger images to minimize the across-experimental difference; an identical scanner system was used for all

participants. Our study is still limited because our measurement cannot be readily compared to the measurement in previous studies

In conclusion, we described the relationship between the 2D:4D ratio and the patients with METH dependence and found that intrauterine exposure to testosterone may influence the development of METH addiction and the characterization of temperament. The potential of the 2D:4D ratio as a biomarker for METH dependence was verified.

Future studies are necessary for investigating the molecular biological mechanism of sex hormones implicated in intrauterine brain development that may characterize temperament to elucidate its relationship with METH dependence.

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**Table 1. Demographic and clinical characteristics of patients with METH dependence (n=40)**

Variables	Statititics
Age	47.57(13.1374)
Age at first METH use	29.8(9.474)
Years of METH use	15.75(13.998)

**Table 2. Difference of 2D:4D ratio between METH addicts and Controls (n=40)**

	Participants		<i>t</i>	<i>p</i>
	Patients(n=40)	Controls(n=50)		
2D:4D right hand	0.941(0.037)	0.961(0.026)	-3.092	0.003**
2D:4D left hand	0.943(0.035)	0.961(0.03)	-2.552	0.012*

\*\*: $p < 0.01$ , \*: $p < 0.05$

Fig.1. Right 2D:4D between METH addicts and Controls

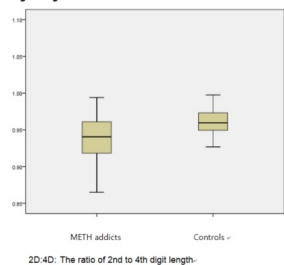


Fig. 1.

Fig. 2. Left 2D:4D between METH addicts and Controls

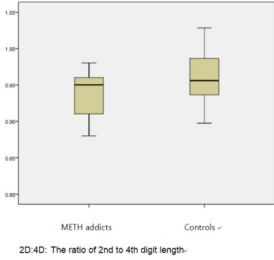


Fig. 2.