Published in final edited form as:

J Med Primatol. 2018 February ; 47(1): 78–80. doi:10.1111/jmp.12318.

2D:4D digit ratio is not a biomarker of developmental programming in baboons (*Papio hamadryas*)

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Abstract

We hypothesized second to fourth hand digit ratio (2D:4D) is a biomarker of developmental programming in three baboon groups: intrauterine growth restriction (7 females, 8 males), exposure during fetal life to synthetic glucocorticoids (4 females, 5 males), and controls (66 females, 20 males). 2D:4D was similar between sexes and groups.

Keywords

intrauterine growth restriction; synthetic glucocorticoids; betamethasone; maternal nutrient reduction

Introduction

There is a need for biomarkers of developmental programming in nonhuman primate experimental models to enable translation to humans. Baboons are an extensively studied model of programming.^{1–9} 2D:4D digit ratio has been suggested as a potential biomarker of programming because larger difference in length between the two fingers is thought to indicate greater prenatal exposure to different hormonal milieus.¹⁰ Higher prenatal androgen levels are, for example, associated with decreased digit ratios.¹¹ Associations have been reported between digit ratio and aggression, occupational interests, social status, eating disorders, risk-taking behavior, and sexual orientation.¹⁰ Offspring of women pregnant during the Dutch Hunger Winter have provided one of the most extensively studied human epidemiology cohorts of developmental programming indicating predisposition to multiple chronic diseases, e.g. cardiovascular disease^{12,13} and obesity.¹⁴ Data from the Dutch Hunger Winter show no association of maternal undernutrition with digit ratio.¹⁵

We tested the hypothesis that 2D:4D digit ratio is a biomarker of programming in three groups of adult baboons (*Papio hamadryas*): [1] intrauterine growth restricted (IUGR)

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offspring of mothers undernourished during pregnancy and lactation; [2] offspring of mothers who received synthetic glucocorticoids (sGC) in late gestation to model a treatment for women threatening premature delivery; and [3] control (CTR) baboons not subjected to experimental programming exposures.

Materials & Methods

Humane care guidelines

All procedures were approved by Texas Biomedical Research Institute Institutional Animal Care and Use Committee and conducted in *Association for Assessment and Accreditation of Laboratory Animal Care* approved facilities. Animals were treated in accordance with the United States Animal Welfare Act.

Animals & housing

Animals (77 females, 33 males; ages 7–22 years) were housed in outdoor social groups (10–16 animals) at Southwest National Primate Research Center, San Antonio, Texas. Baboons were in good health at semi-annual veterinary exams and when studied.

The IUGR group (7 females, 8 males; ages 7–10 yrs) were offspring of mothers who ate 70% feed eaten by *ad libitum* fed CTR in pregnancy and lactation, adjusted for body weight; IUGR offspring were ~13% lower body weight than gestational age and sex-matched controls.¹⁶ The sGC group (4 females, 5 males; ages 10–12 yrs) were offspring of mothers who received three courses of intramuscular (IM) betamethasone phosphate (175 µg/kg day × 2 days) at 0.60, 0.64, and 0.68 gestation (pregnancy days 111/112, 118/119, 125/126), timing equivalent to 24, 26, and 28 weeks of human pregnancy (baboon gestation is 180 days).¹⁷ The CTR group (66 females, 20 males) consisted of baboons not experiencing programming exposures. Detailed methods and phenotypes for IUGR^{1,3,4,6,16,18} and sGC^{5,17,19,20} treatments are published.

Digit and body size measurements

Measurements were taken under ketamine sedation (10 mg/kg IM) by two trained, experienced technicians. Body weight (kg) was measured on a digital scale. Body length (cm) was measured with a tape measure positioned from the back of the head at the parietal and lambdoidal suture intersection to the rump at the largest coccygeal protrusion to the right heel. The second and fourth digits were measured with a sliding caliper. The second digit (2D) of the hand was extended its full length. The fixed caliper jaw was placed on the midpoint of the basal crease. The sliding caliper jaw was extended past the end of the finger, then retracted until it laid gently at the most distal tip of the finger in the midline. Readout was recorded to the nearest 0.01 mm. The measurement was repeated for the fourth digit (4D) on the same hand. All measurements were taken three times and the means used as final values. 2D:4D digit ratio was calculated as 2D length divided by 4D length.

Statistical analysis

Using Pearson's correlation we determined 2D:4D was not associated with age ($p=0.31$), body weight ($p=0.19$), or body length ($p=0.34$); therefore, we did not include these variables

when testing for differences between treatment groups. Two-way ANOVA with post-hoc Sidak's test was performed for differences in 2D:4D between sexes and treatments.

Results

2D:4D was similar between sexes and treatment groups (Figure 1). There was no main effect ($F(5,104)=0.50$, $p=0.78$), nor any effects of sex ($p=0.64$) or treatment ($p=0.90$). Post-hoc tests between IUGR, sGC, and CTR showed no differences between any groups.

Discussion

We found similar 2D:4D ratios in IUGR, sGC, and control baboons. The 110 baboons studied had comparable mean 2D:4D in both sexes as published in two other studies (Table 1).^{21,22} The current study and one other baboon study by Nelson and Shultz²² found no difference between sexes, in contrast to the earliest report from Roney and colleagues.²¹ Nelson and Shultz²² presented an analysis of 2D:4D in a broad array of nonhuman primate taxonomic groups, finding no sex difference in cercopithecine monkey species (baboons and macaques). These findings along with those of the current study suggest lack of sex difference in 2D:4D ratio is a normal feature of baboon populations. Baboons and other Old World monkeys have lower variation in digit ratio than humans, great apes, or New World monkeys.²² The greatest source of known variation in baboon digit ratio is female dominance rank, an inherited trait.^{11,23} Dominance rank data were unavailable in our baboons due to logistical difficulties of measuring rank in a large number of animals living in many different social groups, but we acknowledge rank may be an important factor underlying 2D:4D.

We conclude 2D:4D digit ratio is not associated with sex or treatment in IUGR, sGC, and control baboons. Therefore, 2D:4D digit ratio is not a biomarker of baboon offspring programming by maternal nutrient reduction or sGC administration. This is further supported by the lack of association between maternal undernutrition and digit ratio in humans exposed to the Dutch Huger Winter.¹⁵ The low degree of variation in baboon digit ratio compared to humans and other primate species²² makes 2D:4D an impractical variable to test for differences between experimental groups.

Acknowledgments

Funding from NIH R24 RR021367-01, HD21350, and OD011183. Thanks to Karen Moore, Susan Jenkins, Martha Avila, McKenna Considine, Steve Rios, and Sam Vega for administrative and technical assistance.

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Figure 1.

Table 1

Mean 2D:4D digit ratios for males and females in the current study and two published baboon (*Papio sp.*) studies.

Current study		Roney et al. 2004 ²¹		Nelson & Shultz 2010 ²²	
2D:4D	N	2D:4D	N	2D:4D	N
Male	0.86 ± 0.01 33	0.88 ± 0.01 11	0.85 ± 0.04 11		
Female	0.85 ± 0.01 77	0.83 ± 0.01 21	0.86 ± 0.04 15		