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No sexual dimorphism in human prenatal metacarpal ratios

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ABSTRACT

Background: Ratios of digit lengths are studied intensively as markers of prenatal sex hormone levels.
Aim: Study sexual dimorphism in ratios of metacarpals, which received less attention.
Methods: We studied six metacarpal ratios in deceased human fetuses of ages 10 to 42 weeks.
Results and conclusion: We found no indication of a sexual dimorphism at this early stage of development.

1. Introduction

In humans, the second to fourth digit ratio (2D:4D) — among other digit ratios — is smaller in males than in females [8]. This sexual dimorphism established early in life [2,3,7], is driven by exposure to prenatal sex hormones [6,10], and to some extent influenced by homeobox genes [5,19]. Nevertheless, it is influenced by at least 20 genes that control development of many organ systems including the limb skeleton and the brain [9,20]. Because prenatal environmental conditions — including hormone exposure — can have significant effects on individual morphology, behavior and performance as an adult, the study of variation in digit ratios in humans and primates has received much interest (e.g., [1,8]). While finger ratios have been studied intensively, those of metacarpals have received much less attention. Nevertheless, similar sexual dimorphism has been observed in chimpanzees, gorillas and baboons, as well as in humans, although the dimorphism appeared to be more strongly affected by metacarpal 5 compared to metacarpal 4 [4,11–13,15].

To date, however, no study has been conducted during early development, which would lead to important insights into the developmental stage where the dimorphism emerges (e.g. [3]). Here, we investigate sexual dimorphism in six metacarpal ratios (2M:3M; 2M:4M; 2M:5M; 3M:4M; 3M:5M and 4M:5M) in over 600 deceased and electively aborted human fetuses from two populations, to test if sexual dimorphism already emerges during early fetal development.

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2. Materials and methods

2.1. Study populations

2.1.1. Population 1

Between 1964 and 1974, human fetuses from elective abortions were collected by scientists at the Institute of Dentistry, University of Turku (Finland) to study craniofacial development. For ethical reasons all background information on the mothers has been discarded, leaving only data on the gestation age, sex and size for the majority of the fetuses. Complete fetuses were preserved by the 'clearing and single staining' procedure and kept on glycerin. This technique allows studying skeletal traits by making eviscerated specimens semi-transparent with potassium hydroxide and staining ossified parts with alizarin red. All fetuses were externally evaluated for skeletal malformations (including craniofacial and limb defects) by a pediatric pathologist (LW) and no major abnormalities were reported. Bots et al. [21] did report the presence of a high frequency of cervical ribs and rudimentary 12th ribs. Measurements of the metacarpals were obtained for 182 individuals (95 females and 83 males), aged 10 to 20 weeks of gestation (mean 15.2 weeks ± 2.1). Each fetus' left and right hand was photographed independently and repeatedly with a Canon 300D digital SLR camera. Digital pictures were scaled using a transparent ruler (resolution of 0.1 cm) and analyzed in Image J 1.42q [22]. Metacarpals II to V were

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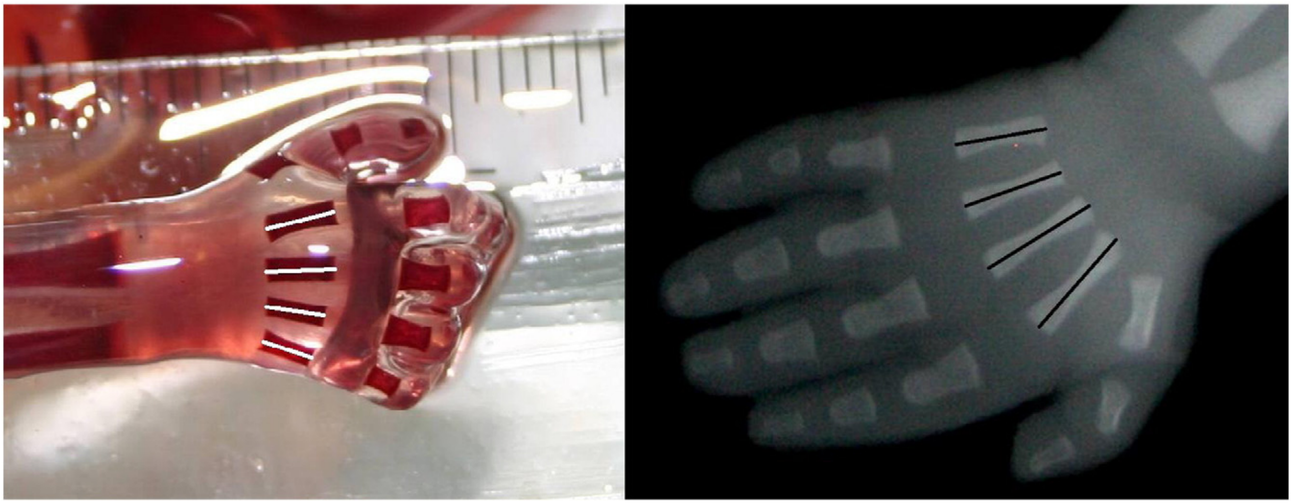

Fig. 1. Measurements of metacarpals in populations 1 and 2 on the basis of photographs of cleared and stained fetuses and X-rays respectively (left and right picture respectively).

measured from the center of the proximal end to the center of the distal end of the bones (Fig. 1). Digits could not be measured for most fetuses because fingers had become rigid such that it was impossible to straighten them for accurate measurement. All measurements were repeated twice independently for each picture to evaluate repeatability (see below).

2.1.2. Population 2

Since 1980, deceased human fetuses presented for autopsy at the VU Medical Centre in Amsterdam (The Netherlands) have been routinely radiographed ventrally and laterally with hands taped in as straight a position as possible (23 mA, 70–90 kV, 4–12 s, Agfa Gevaert D7DW Structurix films). The ventral radiographs of 1195 fetuses that died between 1990 and 2009 were used for this study. To allow digital image analysis, we digitalized these radiographs using a standard set-up with a Canon 300D digital SLR camera positioned in a fixed distance from a glass plate with flash underneath. In total, pictures of 655 male and 540 female fetuses (mean, 28 weeks ± 11 weeks; range, 14–42 weeks) were examined. For the left and right hand of each fetus, the six metacarpal ratios were determined in Image J 1.46. Metacarpals II to V were measured from the center of the proximal end to the center of the distal end of the bones (Fig. 1). Only pictures were included where the hands were in a flat position, leading to measurements for at least one ratio in 264 male and 271 female fetuses. In addition to the metacarpals, digits 2 and 4 were measured (see [3] for details). Measurements were repeated twice independently for each picture (if available) to evaluate repeatability. Data on ethnicity were not available for individual fetuses in either sample, but the patient populations of both samples were predominantly Caucasian. Gestational ages were provided by the gynecologist, based on the time since the first day of the last menstruation (post menstruation).

2.2. Statistical analysis

We first investigated the repeatability of our measurements using a mixed ANOVA model with individual and the interaction between picture and individual (i.e., a nested picture effect within individual) as random effects. Repeatabilities ranged between 0.82 and 0.95 and did not show marked differences between populations. Thus, the metacarpal ratios were estimated with high accuracy.

To investigate sexual dimorphism in each study population, metacarpal ratios (2M:3M; 2M:4M; 2M:5M; 3M:4M; 3M:5M and 4M:5M), and digit ratio 2D:4D for population 2, averaged across the left and right hand, were treated as dependent variables in linear models with sex as fixed factor and age as continuous covariate. The two-way interaction between sex and age was also tested (i.e., an ANCOVA model with different slopes). To investigate covariation in metacarpal and digit ratios, we estimated and tested correlations between the digit and metacarpal ratios after correcting for possible age and gender effects, modeled in the ANCOVAs. Analyses performed separately for left and right hand measurements gave very similar results (data not shown). All analyses were performed in R (version 2.10.1) using the function lm for the ANCOVA models and lmer in the package lme4 for the mixed ANOVA. Descriptive statistics are reported as mean ± SE, and effect sizes of the sexual dimorphism is provided as Cohen's D. For comparison with other studies, sexual dimorphism in 2D:4D and 2M:4M is also provided for both sides separately.

3. Results

Table 1 provides an overview of the ANCOVA model results. No sexual dimorphism was detected in either population, and in none of the six metacarpal ratios (Table 1). Although not significantly so for each test, the metacarpal ratios appeared to decrease with age in population 1 (i.e., between gestation weeks 10–20), and to increase slightly in population 2 (mainly data after an age of 20 weeks of gestation) (see sign of correlation coefficient in Table 1). None of the interactions with sex was significant, indicating that the changes in metacarpal ratio with age were comparable between male and female fetuses (Table 1). Effect sizes were small ranging between −0.14 and 0.14 with an average of 0.037.

Estimated associations and raw data for the M2:M4 ratio in males and females in both populations are provided in Fig. 2 (results for the other ratios were very similar). Because population 2 consisted of deceased fetuses, many of which showed severe congenital abnormalities, we also plotted the data for the fetuses of population 2 which did not show any major abnormalities after medical examination (red symbols in Fig. 2). These observations did not appear to behave differently (Fig. 2).

For the 2D:4D digit ratio in population 2, in contrast, the sexual dimorphism was statistically significant ($F_{1,257} = 10.8$, $p = 0.001$), with 2D:4D being smaller for males (mean = 0.916, SE = 0.002, N = 140) than for females (mean = 0.928, SE = 0.003, N = 120). The 2D:4D decreased with age (slope = −0.0009, $F_{1,257} = 18.4$, $p < 0.0001$), and this decrease was similar for male and female fetuses (i.e., no significant interaction between sex and age, $F_{1,256} = 0.01$, $p = 0.93$). The 2D:4D did not correlate with any of the metacarpal ratios after