

# Masculinized Finger Length Patterns in Human Males and Females with Congenital Adrenal Hyperplasia

Windy M. Brown,\* Melissa Hines,†‡ Briony A. Fane,† and S. Marc Breedlove§<sup>1</sup>

\*Department of Psychology, University of California, Berkeley, Berkeley, California 94720;

†Department of Psychology, City University, London, United Kingdom EC1V 0HB;

‡Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, California 90095; and §Neuroscience Program, Department of Psychology and Department of Zoology, Michigan State University, East Lansing, Michigan 48824

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The ratio of the length of the second digit (2D) to the length of the fourth digit (4D) is greater in women than in men. Since androgens are involved in most somatic sex differences and since the sexual dimorphism in 2D:4D is stable from 2 years of age in humans, it was hypothesized that finger length pattern development might be affected by early androgen exposure. Human females with congenital adrenal hyperplasia (CAH) are exposed prenatally to higher than normal levels of adrenal androgens, providing an opportunity to test the effects of early androgen exposure on digit ratios. The 2D:4D was calculated for females with CAH, females without CAH, males with CAH, and males without CAH. Females with CAH had a significantly smaller 2D:4D on the right hand than did females without CAH. Males with CAH had a significantly smaller 2D:4D on the left hand than did males without CAH. A subset of six males with CAH had a significantly smaller 2D:4D on both hands compared with their male relatives without CAH. These results are consistent with the idea that prenatal androgen exposure reduces the 2D:4D and plays a role in the establishment of the sex difference in human finger length patterns. Finger lengths may therefore offer a retrospective marker of perinatal androgen exposure in humans.

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<sup>1</sup> To whom all correspondence should be addressed at Neurosciences Program, Psychology Research Building, Michigan State University, East Lansing, MI 48824. Fax (517) 432-1674. E-mail: breedsms@msu.edu.

In humans, the ratio of the index finger to the ring finger (2D:4D) is sexually dimorphic. Women have a larger 2D:4D on average than do men (George, 1930; Manning, Scott, Wilson, and Lewis-Jones, 1998). This sex difference in finger length patterns was first reported more than 100 years ago (Ecker, 1875). A recent replication of this sex difference in a cross-sectional sample of humans from a given population (Liverpool, England) reported stable means of 2D:4D for males and females from 2 years of age through adulthood (Manning *et al.*, 1998, Manning, 2002). Since the masculinizing and defeminizing effects of androgens appear to be involved in most somatic sex differences reported thus far in the literature (Breedlove, Cooke, and Jordan, 1998), it appears likely that the 2D:4D sexual dimorphism may also be due to androgens. The 2D:4D sex difference may, however, arise from some other biological mechanism that differs between the sexes. For instance, an early report suggested that the longer index finger in women may be due to sex-influenced inheritance of a gene involved in skeletal structure that is dominant in women and recessive in men (Winchester, 1976). More recent research has emphasized the role that the Y chromosome itself may play in sexual differentiation and resultant sex differences (Arnold, 1996). It is also unclear when androgens are acting, if indeed they are responsible for digit length masculinization. The consistency of the 2D:4D sex difference across age in humans suggests an organizational, developmentally early mode of action. Similarly, rear paw 2D:4D is greater in female than in male mice, and this sex difference is established before

puberty (Brown, Finn, and Breedlove, 2002), which also suggests that adult androgens are not responsible for the sex difference. However, Manning and colleagues' study also reported a significant negative correlation between adult circulating testosterone levels and 2D:4D in men, which suggests that adult levels of testosterone may affect finger length patterns in humans.

One test of the hypothesis that androgens act during development to masculinize finger length patterns is to measure the finger length patterns of people who have been prenatally exposed to different levels of androgens. Females with congenital adrenal hyperplasia (CAH) provide such an opportunity. CAH is an autosomal recessive condition that results in a disruption of the glucocorticoid synthesis pathway in the adrenal glands. Lacking an enzyme necessary for glucocorticoid production, the glucocorticoid precursor 17-hydroxyprogesterone builds up in individuals with CAH and is converted into androstenedione instead. The lack of circulating glucocorticoids causes the hypothalamus to release more ACTH in the body's homeostatic effort to maintain normal corticosteroid levels, which in turn triggers the production of even more androstenedione. Abnormally high adrenal androgen secretion results (Griffin and Ojeda, 2000).

CAH is the most common cause of virilization in female newborns and can masculinize the external genitalia to such an extent that the newborn may be thought to be a genetic male, although an ambiguous intersex phenotype is more common (Griffin and Ojeda, 2000). Salt losing crises in infancy often lead to the diagnosis, especially in males with CAH because no obvious alterations in genital morphology call attention to the condition. It is usually diagnosed at, or soon after, birth in both males and females. Cortisol treatment is undertaken immediately on diagnosis to regulate electrolytes, which also serves to normalize sex hormone levels postnatally. Since diagnosis is usually around birth, differences in morphology and behavior between individuals with and without CAH can presumably be attributed to differences in prenatal hormone levels. This disorder has therefore provided researchers with the opportunity to investigate the effects of prenatal androgens on many sexually dimorphic characteristics in humans.

Several lines of evidence suggest that the external genitalia are not the only part of the body to be masculinized by excessive prenatal androgen levels. Compared with their unaffected sisters, girls with CAH play more with boy-typical toys, prefer boys as playmates, and prefer boy-typical activities (Ehrhardt, Ep-

stein, and Money, 1968; Dittman, Kappes, Kappes, Borger, Stegner, Willig, and Wallis, 1990; Berenbaum & Hines, 1992; Hines and Kaufman, 1994). There is also some evidence of alterations in sexual orientation and tendencies to aggression in females with CAH, although these effects are less well established than those on childhood play (Collaer and Hines, 1995). These behavioral changes suggest that the brains of these individuals have been masculinized as well as their external genitalia. Evidence for similar effects in males is less straightforward. Some studies suggest males with CAH display hypomasculinized behavior (Hines and Kaufman, 1994), some hypermasculinized behavior (Ehrhardt and Baker, 1974), and some no difference from control males (see Collaer and Hines (1995) for discussion).

Interestingly, the same subfamilies of genes that are involved in genital development, the *Hoxa* and *Hoxd* genes, are also involved in digit development (Peichel, Prabhakaran, and Voght, 1997). This shared genetic pathway lends further support to the notion that prenatal androgen might affect 2D:4D ratios. Since the development of genital structures is influenced by androgen, the genes coding for genital development must be directly or indirectly modulated by androgen exposure. Therefore the development of other structures influenced by these genes, such as the digits, might also be modulated by androgen.

Females with CAH offer a straightforward test of the hypothesis that prenatal androgens can affect 2D:4D. If these females have a smaller 2D:4D than control females, then the hypothesis can be retained for further testing.

## MATERIALS AND METHODS

Subjects for this study were recruited through pediatric endocrinologists at Great Ormond Street Hospital, London, England, and through the CAH support group in the United Kingdom. Individuals with CAH and their unaffected relatives were taking part in a study of physical, cognitive, and personality development. As part of this study, they had photocopies made of their hands. The ventral surfaces of both hands of 13 females with CAH aged 7–44 years (average = 15), 44 control females without CAH aged 12–44 years (average = 18), 16 males with CAH aged 5–21 years (average = 11), and 28 males without CAH aged 9–34 years (average = 15) were photocopied. A male relative who did not display CAH was available

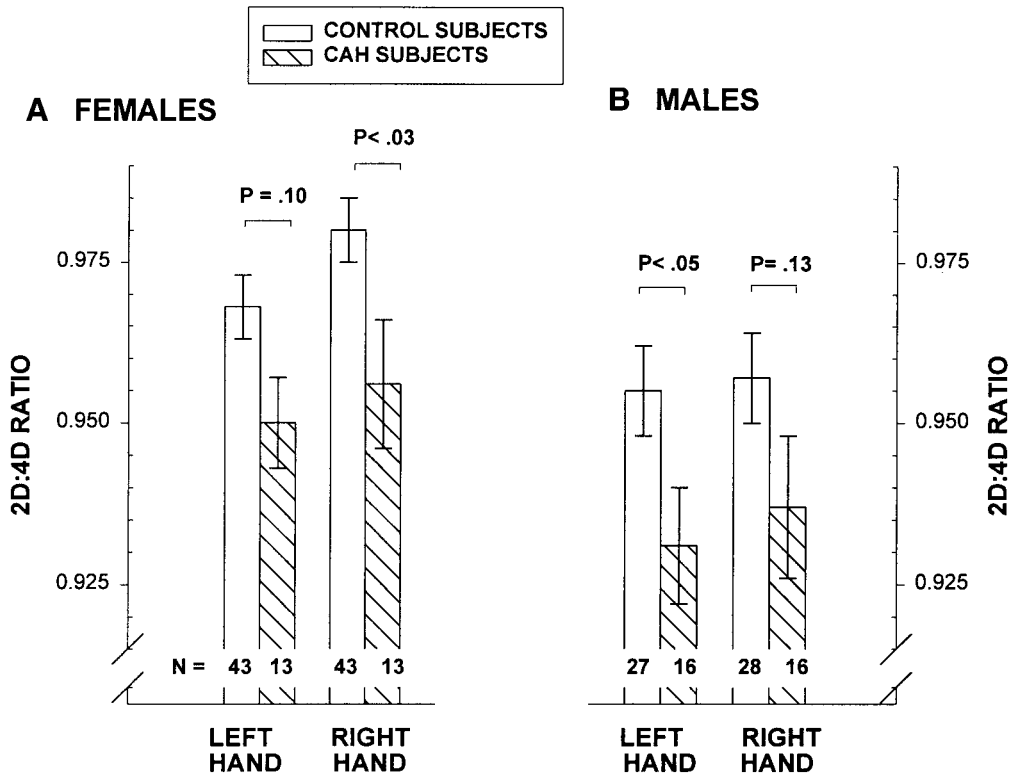
to act as a control for 6 of the male participants with CAH.

The photocopies were coded to conceal group membership before a researcher measured the length of the second and fourth digits to the nearest 0.5 mm using a transparent ruler. The index finger was measured from the single crease at the base of the finger to the tip. The ring finger was measured from the more proximal of the two wrinkles at the base of the finger to the tip. Occasionally the photocopied image of the tip or base of a finger was not clear, which prevented obtaining a 2D:4D for that particular hand from that particular subject. A 2D:4D ratio was calculated for both hands of each subject by dividing the length of the index finger (2D) by the length of the ring finger (4D). Student's *t* tests or matched-pair *t* tests were used to evaluate group differences, with only two-tailed *P* values reported. Effect sizes (*d* values) were also calculated for significant group differences and their evaluation based on guidelines from Cohen (1988).

## RESULTS

On the right hand, females with CAH had a significantly more masculine-typical 2D:4D than did control females ( $P < 0.03$ ), a difference of medium effect size (0.7). On the left hand, the difference between females with and without CAH did not reach significance ( $P < 0.10$ ) although it was in the same direction. There were no differences between females with CAH and control females in the absolute length of any of the four fingers measured (all *P*'s  $> 0.25$ ), only in the ratio of the length of 2D to 4D. In males, the difference on the right hand between participants with CAH and controls was not significant ( $P = 0.13$ ). The left-hand 2D:4D, however, was significantly smaller in males with CAH than in controls ( $P < 0.05$ ). This difference also reflects a medium effect size (0.6) (Fig. 1).

For the subset of six males with CAH with unaffected male relatives to serve as controls, a matched-pair *t* test showed that the 2D:4D of the males with CAH (left =  $0.9151 \pm 0.041$ , right =  $0.9069 \pm 0.048$ )



**FIG. 1.** (A) Mean finger length ratios of females with CAH and control females for both the left and right hands. Females with CAH have a significantly smaller 2D:4D on the right hand than do control females. (B) Mean finger length ratios of males with CAH and control males for both the left and right hands. Males with CAH have a significantly smaller 2D:4D on the left hand compared with control males. Error bars represent standard errors of the means; all *P* values are two-tailed.

was significantly smaller than that of their relatives, both on the left ( $0.9528 \pm 0.039$ ,  $P = 0.01$ ) and the right ( $0.9569 \pm 0.038$ ,  $P < 0.04$ ) hands. Effect sizes are large for both the right (1.0) and left (0.9) hands (Fig. 2).

The sex difference in 2D:4D reported in previous studies was also replicated in the participants without CAH. Females without CAH had a significantly larger 2D:4D on the right hand ( $0.9810 \pm 0.032$ ) than did males without CAH ( $0.9572 \pm 0.0375$ ,  $P < 0.006$ ). This difference reflects a medium effect size of 0.7. On the left hand, there was not a significant difference between control females ( $0.968 \pm 0.005$ ) and control males ( $0.955 \pm 0.007$ ,  $P < 0.14$ ). The sex difference in 2D:4D among the control subjects seemed to be due primarily to a longer ring fingers in males ( $P$ 's  $< 0.03$ ), as the length of the index fingers did not differ between the sexes. There was no significant sex difference in 2D:4D between females with CAH and males with CAH on either the right-hand ( $P = 0.23$ ) or the left-hand ( $P = 0.08$ ) comparisons, although in both cases male CAH ratios tended to be smaller than fe-

male CAH ratios as evidenced by the means displayed in Fig. 1. In addition, females with CAH did not differ significantly from males without CAH on either the right ( $P = 0.98$ ) or left ( $P = 0.88$ ) hand.

## DISCUSSION

The reduced 2D:4D in females with CAH compared with control females is consistent with the hypothesis that prenatal androgens can reduce this finger length ratio, and are responsible for the sex difference in 2D:4D in populations without CAH. Had the 2D:4D of females with CAH been identical to that of control females, this hypothesis would have been rejected. The present results are incompatible with the competing hypothesis that some direct genetic effect from the Y chromosome is responsible for the sex difference in 2D:4D (e.g., Arnold, 1996), since CAH females do not possess a Y chromosome. XY humans with complete androgen insensitivity would offer a further test of whether androgen is the hormone responsible for the

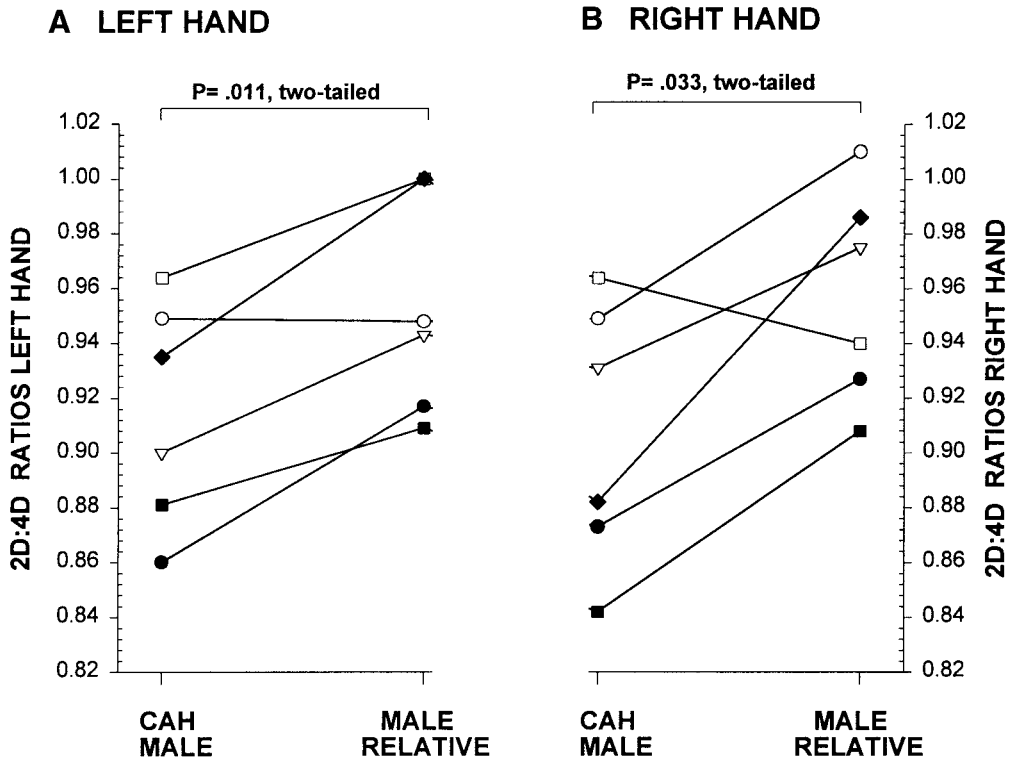


FIG. 2. (A) Individual values of left-hand finger length ratios for six males with CAH and their six matched, male relatives. (B) Individual values of right-hand finger length ratios for the same six male participants and their male relatives. Symbols for each pair of relatives are consistent between the two graphs. The males with CAH have a significantly smaller 2D:4D than do control males on both the left and right hands.

sex difference in 2D:4D. If such individuals have a feminine 2D:4D, then androgens would be implicated, but if they have a masculine 2D:4D, then direct genetic mechanisms might be at work.

Alternatively, it is possible that some other, nonandrogenic, hormonal consequence of CAH, such as increased exposure to ACTH or decreased exposure to corticosteroids, decreased 2D:4D in these subjects. To reconcile such a mechanism with the sex difference in 2D:4D would require that humans also display a perinatal sex difference in ACTH (with males exposed to more of the hormone than females) or in corticosteroids (with males exposed to less of the hormone than females), but we know no evidence for either. This theory of corticosteroid influence on the 2D:4D would explain the lack of a significant difference in 2D:4D between CAH male and CAH female fetuses, since they may be exposed to similar amounts of corticosteroids and ACTH. If androgens were the primary factor producing the sex difference in 2D:4D one might expect males with CAH to have more masculine ratios than females with CAH, because the males are exposed to more fetal androgen than their female counterparts, at least during sexual differentiation of the genitalia. Yet the lack of a significant sex difference in the 2D:4D of individuals with CAH should be interpreted with caution in light of the small sample size of this study.

Likewise, we cannot be sure that differences between females with CAH and control females are due only to prenatal mechanisms. Although every attempt is made to normalize hormone levels once a diagnosis of CAH is made, and this diagnosis is usually made at or around birth, we cannot rule out the possibility that participants with CAH in this study were exposed to abnormal hormone levels after birth affecting finger length patterns. The developmental timetable of the phalanges is compatible with a prenatal influence on the 2D:4D, since both the metacarpals and the phalanges attain adult relative length rankings during human fetal development (Garn, Burdi, Babler, and Stinson, 1975). Manning and colleagues' cross-generational study demonstrated stability in the 2D:4D sex difference from 2 years (the youngest age measured) to adulthood, which again suggests that early developmental factors lead to permanent sexual dimorphism in the 2D:4D. Unlike some other sexually dimorphic characteristics that arise under the activating influence of hormones later in life, such as breast development, the 2D:4D does not seem to be altered by hormonal events throughout postnatal life such as puberty (Manning, 2002). But these data do not rule

out the possibility that sex differences in infant testosterone levels (e.g., Hughes, Coleman, Ahmed, Ng, Cheng, Lim, and Hawkins, 1999) may continue to act neonatally to produce the sex difference in 2D:4D by 2 years of age.

The significantly lower 2D:4D on both the left and right hands in males with CAH compared with their male relatives further supports the hypothesis that perinatal hormones of some sort affect finger length patterns. It also draws attention to the potential influence of other factors on the 2D:4D. Presumably the larger effect sizes in the matched-pair tests of related males, compared with those of the independent *t* tests between individuals with CAH and unrelated individuals without CAH, result from controlling for genetic and/or shared intrauterine influences on finger length patterns when comparing relatives. Some of the individual variation in finger length patterns when comparing unrelated individuals, therefore, could arise from these factors. This would explain why such large sample sizes are often necessary to see group differences in the 2D:4D. This influence could be either a direct genetic mechanism controlling finger growth or some other maternal factor that either directly or indirectly alters finger length patterns. Note that genetic and hormonal influences are not mutually incompatible—genes may affect 2D:4D by affecting hormone production and/or responsiveness.

We did not predict a priori that males with CAH would have hypermasculinized finger length patterns. Little evidence exists for hypermasculinization of other characteristics known to be androgen-sensitive in males with CAH, despite the fact that the disorder causes excessive adrenal androgen production. For example, some studies indicate males with CAH show unaltered male-typical play, while others indicate decreased male-typical play (Collaer and Hines, 1995). Several explanations have been offered for the normal or under-masculinization of males with CAH. First, androgen receptors may be saturated in the normal male fetus so that overproduction of androgens is unable to further masculinize sensitive tissues. Alternatively, the male fetus may maintain circulating androgen levels within a specific range so that extra adrenal androgen produced in males with CAH is compensated for by a decrease in the output of gonadal androgen.

If males with CAH are indeed exposed to normal or below-normal levels of androgen during some fetal stages, how can the present finding of smaller, more masculine 2D:4Ds in males with CAH be explained? One possibility, discussed above, is that hormones

other than androgens are responsible for the reduced finger length ratios in individuals with CAH. Alternatively, males with CAH may indeed experience higher than normal androgen exposure at a specific stage of development when fingers, but not genitalia (Brookes and Zietman, 1998) or play-related structures, are androgen-responsive. The notion that androgenization may be spatially and temporally specific, rather than global, has been proposed by Woodson and Gorski (1999) to account for structural sex differences in the rodent brain, and by McFadden (2002) to explain sex differences in the auditory system. If males with CAH in fact regulate gonadal androgen production in compensation for excess adrenal androgen, the levels of circulating androgen in CAH male fetuses may be complex, so that they may see more androgen than other males at some stages of development and less androgen at other stages. Females, of course, do not normally display such compensatory mechanisms to regulate fetal androgens because they normally produce little of these sex hormones. CAH female fetuses therefore lack the equivalent means to decrease androgen levels, and thus display virilization along more dimensions than do males with CAH.

In support of the notion that androgens affect the 2D:4D of males with CAH, prenatal androstenedione levels were found to be higher in fetuses with CAH than in those without CAH, for both males and females (Wudy, Dörr, Solleder, Djalali, and Homoki, 1999). Although 17-hydroxyprogesterone has traditionally been used for the prenatal diagnosis of CAH, at least one other report shows accurate prenatal diagnosis of CAH in both males and females based on elevated androstenedione (Dörr and Sippell, 1993).

One report that also must be addressed is the negative correlation between adult testosterone levels and 2D:4D in men (Manning *et al.*, 1998). If androgens act exclusively during the early prenatal environment to masculinize finger length patterns, one might not expect to see such a correlation in adult males. A possible explanation for this finding may lie in the stability of individual differences in sex hormone levels across age. Individual differences, both within and between the sexes, exist in sex hormone levels at birth (Sakai, Baker, Jacklin, and Shulman, 1991; Marcus, Maccoby, Jacklin, and Doering, 1985) and in adulthood (Couwens, Knussmann, and Christiansen, 1986). It is possible that a male fetus that produces high normal androgen levels may continue to exhibit higher androgen levels than other males in adulthood. This would explain the reported negative correlation between adult testosterone levels and finger length patterns

without implicating adult androgen as a factor influencing the 2D:4D. Longitudinal studies to test this hypothesis have not yet been conducted.

To our knowledge, this is the first report of a known difference in prenatal androgen levels in females that is accompanied by a difference in later 2D:4D. To date, this link has only been implied, as with the 2D:4D differences observed between heterosexual and homosexual women (Williams, Pepitone, Christensen, Cooke, Huberman, Breedlove, Breedlove, Jordan, and Breedlove, 2000). In this particular example, because it was thought that digit length ratios are determined prenatally, group differences in finger length patterns between gay and straight women were assumed to reflect differential exposure to prenatal androgens. Significant differences between individuals with and without CAH, who differ in their prenatal androgen exposure, provide some support for this conjecture. Failure to see an effect of CAH on 2D:4D would have argued against the hypothesis.

Thus 2D:4D ratios may provide a useful retrospective marker for early androgen exposure, making it possible to correlate such exposure with human behavior. Thus far, finger length patterns have been found to correlate significantly with factors that range from sperm count (Manning *et al.*, 1998), and sexual orientation (Williams *et al.*, 2000), to personality characteristics such as assertiveness in women (Wilson, 1983). Because 2D:4D measures are non-invasive and readily obtained, they may allow additional correlations between early androgen and human behavior. In addition, if the sensitive period for hormonal modulation of finger length patterns during development can be defined, it may provide insight into the etiology of disease predispositions that correlate with adult 2D:4Ds, such as risk for myocardial infarction in men (Manning, 2001).

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