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Genetic and environmental influences on pubertal hormones in human hair across development

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ABSTRACT

Puberty is a complex biopsychosocial process that can affect an array of psychiatric and medical disorders emerging in adolescence. Although the pubertal process is driven by neuroendocrine changes, few quantitative genetic studies have directly measured puberty-relevant hormones. Hair samples can now be assayed for accumulation of hormones over several months. In contrast to more conventional salivary measures, hair measures are not confounded by diurnal variation or hormonal reactivity. In an ethnically and socioeconomically diverse sample of 1286 child and adolescent twins and multiples from 672 unique families, we estimated genetic and environmental influences on hair concentrations of testosterone, DHEA, and progesterone across the period of 8–18 years of age. On average, male DHEA and testosterone were highly heritable, whereas female DHEA, progesterone, and puberty were largely influenced by environmental components. We identified sex-specific developmental windows of maximal heritability in each hormone. Peak heritability for DHEA occurred at approximately 10 years of age for males and females. Peak heritability for testosterone occurred at age 12.5 and 15.2 years for males and females, respectively. Peak heritability for male progesterone occurred at 11.2 years, while the heritability of female progesterone remained uniformly low. The identification of specific developmental windows when genetic signals for hormones are maximized has critical implications for well-informed models of hormone-behavior associations in childhood and adolescence.

1. Introduction

1.1. Overview

Puberty involves two distinct periods of hormonal changes marked by rising hormone levels: adrenarche and gonadarche (Patton and Viner, 2007). Adrenarche and gonadarche are biologically and developmentally dissociable processes characterized by maturation of the hypothalamic-pituitary-adrenal (HPA) and −gonadal (HPG) axes, respectively (Saenger and Dimartino-Nardi, 2001). Specifically, adrenarche begins with the expansion of the inner layer of the adrenal cortex, the zona reticularis, which causes a subsequent increase in dehydroepiandrosterone (DHEA) and its sulphate ester (DHEA-S; Hui et al., 2009). The typical onset of adrenarche is between six and nine years of age in females, and begins approximately one year later in males (Blakemore et al., 2010). Gonadarche begins approximately two years after adrenarche onset with the increase of sex hormones, including testosterone and progesterone. In both boys and girls, rising concentrations of DHEA cause the onset of body odor and pubic hair growth, while rising sex hormones drive the emergence of secondary sex characteristics (Havelock and Auchus, 2004; Hiort, 2002). However, hormone levels are not synonymous with somatic metrics of pubertal development, such as Tanner stages, as hormones are present pre- and post-puberty, and there is overlap in hormone concentrations across pubertal stages.

The extent to which genetic variation accounts for individual differences in the hormonal outputs of adrenarche and gonadarche is unclear. Quantitative genetic designs use genetic similarities between relatives (e.g., twins) to disentangle genetic and environmental effects on variation in an outcome. Although the intuition might be that a biological variable such as hormone levels is strictly heritable, it is possible that a highly constrained set of genes causes the typical rise in hormone levels, while variation about this average is entirely due to environmental input. Indeed, some level of environmental influence is

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to be expected, as pubertal hormones respond to physiological (Hoffman et al., 1996) and psychological stress (Lennartsson et al., 2012). The current paper reports results from quantitative genetic models of pubertal development, testosterone, progesterone, DHEA, and their covariation, in a population representative sample of child and adolescent twins.

1.2. Prior quantitative genetic studies

Previous twin studies have identified significant additive genetic influences on adolescent testosterone for both sexes, with three out of five studies indicating higher heritability in males (Harden et al., 2014b; Harris et al., 1998; Hoekstra et al., 2006; Koenis et al., 2013; Van Hulle et al., 2015). A handful of previous studies indicate that variation in DHEA levels in adolescence contain a large heritable component in males and females (Li et al., 2016; Van Hulle et al., 2015). Similarly, pubertal development, as measured using secondary sex characteristics, has been estimated to be at least 60% heritable in both sexes (Harden et al., 2014b; Hoekstra et al., 2006; Mustanski et al., 2004).

Many of the previous studies included participants spanning the adolescent age range, but age-specific sex differences in biosynthetic pathways suggest that the heritability of hormonal levels may change with development. For example, DHEA is the primary precursor to testosterone biosynthesis for pre-pubertal children and for females across the lifespan, but not for post-pubertal males (Granger et al., 1999). This likely reflects the fact that testosterone switches from primarily adrenal to gonadal in origin during puberty for males only. In support of developmental specificity of genetic effects, the heritability of testosterone was found to increase for males (64%–78%) and decrease for females (70%–51%) from ages 9–12 (Koenis et al., 2013). The key research question, then, is whether different estimates of heritability are obtained across adolescence. This research goal can be contrasted with previous studies that described an aggregate estimate of adolescent heritability. Identifying ages at which disparate heritability estimates are obtained may mark biologically relevant components of the pubertal transition that uniquely predict adolescent behavior.

1.3. Measurement of hormones in hair

Quantitative genetic research on hormone levels is complicated by measurements that reflect state- and trait-specific processes. DHEA, testosterone, and progesterone all display diurnal patterns characterized by peak levels in the morning, followed by a steady decline across the day (Granger et al., 2003; Hucklebridge et al., 2005; Liening et al., 2010; Matchock et al., 2009). There is also variation in hormones across days; one previous study estimated the correlation between testosterone samples taken at the same time of day two days apart at 0.62 (Harden et al., 2016). Although multiple salivary or blood samples can be collected to estimate individual differences in basal hormone levels, this can be costly and may decrease participant compliance.

Hair sampling is a recently developed method that provides a measure of long-term (i.e., several months) free hormone output using a single, non-invasive sample (Gao et al., 2015). Each centimeter of hair is thought to reflect 1 month of hormone accumulation, given an average growth rate of 1 cm per month (Wennig, 2000). Indeed, the association in humans (age range: 21–53) between a 1-cm hair sample and salivary cortisol collected three times daily over a 1-month period was highest when the salivary average included all 4 weeks, and gradually decreased as a function of the number of weeks excluded from the average (Short et al., 2016). This supports the model of hair as a marker of accumulated hormone exposure. Hair cortisol has high test-retest reliability across wide intervals (e.g., $r = 0.73$ across 1 year in a sample with mean age = 30.6; Stalder and Kirschbaum, 2012) but is not associated with salivary measures of reactive cortisol, diurnal slope, or the cortisol awakening response (Grass et al., 2015, [mean participant age = 25]; Short et al., 2016). Other hair hormones have yet to be comprehensively evaluated with regard to intensive salivary measurements.

1.4. Current study

The current study sought to identify developmentally-specific and sex-specific genetic and environmental etiologies of hair biomarkers of testosterone, progesterone, and DHEA in a population representative sample of child and adolescent twins. Based on results from previous twin studies, we hypothesized that testosterone and DHEA would be more heritable in males overall, and generally expected genetic influences on hormones to differ across adolescence.

2. Material and methods

2.1. Participants

Participants were drawn from the Texas Twin Project, a population-based study of school-aged twins in central Texas (Harden et al., 2013). Parents of twin families were contacted by mail and invited to participate in an in-lab study. The current study draws from a final sample of $n = 1286$ individual twins (from 672 unique families) who provided hair samples. Repeat observations were available for 111 participants, for a total of $i = 1397$ (813 female) non-missing observation points. The twins were in grades 3 through 12 and ranged in age from 7.80 to 19.47 years ($M = 12.34$, $SD = 2.77$). Two families had repeat triplets with two observations missing for the repeat visit (contributing 5 pairs each),[1] one family had quadruplets (6 pairs), 24 families had triplets (3 pairs), 3 families had triplets with two missing observations (2 pairs), one family had two sets of twins (2 pairs), and 61 pairs were repeat observations (2 pairs), for a total of 798 twin pairs (266 monozygotic [MZ] pairs [108 male, 158 female] and 532 dizygotic [DZ] pairs [112 male, 148 female, and 272 opposite-sex]). Both twins provided hair specimens for 681 pairs out of the 798 twin pairs. Thirty-one potential participants were excluded on the basis of reported oral contraception use (see Supplement S1.2. for effects on hormone levels) and eight potential participants were excluded for reported endocrine problems (numbers not included in totals above). Sixty-three percent (63%) of the twins identified as non-Hispanic White, 18.6% identified as Hispanic/Latino, 4.2% identified as African American, and 14.2% identified as another race/ethnicity. Of the participating families, 33.4% reported receiving some form of means-tested public assistance (e.g., food stamps) since the twins' birth.

2.2. Measures

2.2.1. Zygosity

Opposite-sex twin pairs were classified as DZ. Same-sex twin pair zygosity was assessed using responses to ratings about the twins' physical similarities (e.g., facial appearance). High school aged twins, parents, and two research assistants completed the ratings. Parents and high school aged twins additionally rated how often the twins are mistaken for one another. These ratings were entered into a latent class analysis (LCA) that was used to obtain zygosity classifications. LCA has been reported to accurately determine zygosity > 99% of the time (Heath et al., 2003). In the present study, for a subset of 153 twin pairs that were genotyped, LCA accurately determined zygosity > 95% of the time.

[1] As twin models in M*plus* are specified to examine pairwise combinations (e.g., Twin 1 with Twin 2) families with repeat observations, triplets, quadruplets or multiple twin sets were analyzed as multiple pairwise combinations. In the case of triplets, this was achieved by examining three pairwise associations: Twin 1 with Twin 2; Twin 2 with Twin 3; Twin 1 with Twin 3.