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The role of testosterone in coordinating male life history strategies: The moderating effects of the androgen receptor CAG repeat polymorphism

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ABSTRACT

Partnered fathers often have lower testosterone than single non-parents, which is theorized to relate to elevated testosterone (T) facilitating competitive behaviors and lower T contributing to nurturing. Cultural- and individual-factors moderate the expression of such psychobiological profiles. Less is known about genetic variation's role in individual psychobiological responses to partnering and fathering, particularly as related to T. We examined the exon 1 CAG (polyglutamine) repeat (CAGn) within the androgen receptor (AR) gene. AR CAGn shapes T's effects after it binds to AR by affecting AR transcriptional activity. Thus, this polymorphism is a strong candidate to influence individual-level profiles of "androgenicity." While males with a highly androgenic profile are expected to engage in a more competitive-oriented life history strategy, low androgenic men are at increased risk of depression, which could lead to similar outcomes for certain familial dynamics, such as marriage stability and parenting. Here, in a large longitudinal study of Filipino men (n = 683), we found that men who had high androgenicity (elevated T and shorter CAGn) or low androgenicity (lower T and longer CAGn) showed elevated likelihood of relationship instability over the 4.5-year study period and were also more likely be relatively uninvolved with childcare as fathers. We did not find that CAGn moderated men's T responses to the fatherhood transition. In total, our results provide evidence for invested fathering and relationship stability at intermediate levels of androgenicity and help inform our understanding of variation in male reproductive strategies and the individual hormonal and genetic differences that underlie it.

1. Introduction

Among species exhibiting biparental care, testosterone (T) is an important physiological mediator of life history trade-offs between competitive, mating-related investments and those devoted to parenting (Archer, 2006; Bribiescas, 2001; Bribiescas et al., 2012; Flinn et al., 2012; Gettler, 2014, 2016; Gray et al., 2016; Puts et al., 2015; Rilling, 2013; Roney and Gettler, 2015; Storey and Ziegler, 2016; van Anders et al., 2011; van Anders, 2013). The applicability of this model to humans is supported by the finding that human males often have lower T in the context of committed relationships and as they transition to fatherhood (Alvarado et al., 2015; Edelstein et al., 2015; Gray et al., 2002, 2006; Gettler et al., 2011, 2015; Mascaro et al., 2013; Muller et al., 2009; Saxbe et al., 2016; van Anders and Watson, 2007). Evidence has shown that fathers' T is lowest when they are invested in childcare (Alvergne et al., 2009; Edelstein et al., 2016; Gettler et al., 2011, 2015; Mascaro et al., 2013; Weisman et al., 2014), while lower basal T as well as acute and diurnal declines in T are linked to sensitive, nurturing behavior and relationship investment (Endendijk et al., 2016; Fleming et al., 2002; Kuo et al., 2015; Saxbe et al., 2016; Storey et al., 2011; van Anders et al., 2012; Weisman et al., 2014). Taken together, this research points to T and changes in T (over multiple time scales) as important components of men's transition from competitive-mating to parenting-related behaviors (Archer, 2006; Flinn et al., 2012; Gettler, 2014, 2016; Gray and Anderson, 2010; Gray et al., 2016; Rilling, 2013; Roney and Gettler, 2015; Storey and Ziegler, 2016; van Anders et al., 2011; van Anders, 2013).

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Accumulating evidence for a role of T in coordinating reproductive strategies and life history transitions in human males has also revealed extensive within- and between-population variation in these relationships. To date, studies have primarily explored the role of cultural factors, such as models of fatherhood (Muller et al., 2009) and polygyny (Gray, 2003; Gray et al., 2007), socioeconomic factors (Jasienska et al., 2012), and individual factors, such as sociosexuality, sensation seeking, and age (McIntyre et al., 2006; Mazur, 2014; Perini et al., 2012; Puts et al., 2015; van Anders and Goldey, 2010), as moderators of these social neuroendocrine profiles. Apart from the widely-researched oxytocinergic system (Bakermans-Kranenburg and van Ijzendoorn, 2008; Feldman et al., 2012, 2013), comparatively little is known about the role of genetic variation in individual physiological and behavioral responses to partnering and parenting among human males. One particularly promising locus for affecting such relationships is the exon 1 CAG (polyglutamine) repeat within the androgen receptor (AR) gene. The AR is the primary receptor to which T and other androgenic hormones bind, leading to downstream physiological effects. The number of AR CAG repeats (CAGn), between eight and thirty-seven in healthy men, has been inversely associated with AR transcriptional activity, and is linked to a range of androgenic somatic and behavioral traits (Ryan and Crespi, 2012). For example, shorter CAGn has been correlated with reduced body fat (Campbell et al., 2007; Zitzmann et al., 2003) and greater upper body strength (Simmons and Roney, 2011).

Past work has similarly suggested that CAGn may moderate relationships between men's T and their personality, behavioral patterns, and mood. Men with short CAGn and elevated T score particularly high on measures of impulsiveness (Aluja et al., 2015) as well as risk taking behavior (Vermeersch et al., 2010). Young men with shorter CAGn also show more pronounced short-term spikes in T during interactions with females (Roney et al., 2010) and report higher self-confidence in competitive contexts (Eisenegger et al., 2016). Recent research among pastoralists and foragers in Tanzania showed that men with shorter CAGn engaged in more aggressive behavior and had a greater number of children than longer CAGn men (Butovskaya et al., 2015), though CAGn has not been linked to such fertility outcomes in all studies (Gray et al., 2009; Rajpert-De Meyts et al., 2002; von Eckardstein et al., 2001). In India, violent offenders had shorter CAGn, on average, than non-criminal controls (Rajender et al., 2008), and, in a separate study, Chinese men with shorter CAGn tended to engage in less prosocial behavior in a laboratory-based economic game, though this did not replicate in Israeli men (Chew et al., 2013). Consistent with the extensive research on the effects of T on vertebrate male life history strategies (Bribiescas, 2001; Bribiescas et al., 2012; Hau, 2007; Ketterson et al., 1992) and human psychobiology (Archer, 2006; Carré and Olmstead, 2015; Flinn et al., 2012; Gettler, 2014; Gray et al., 2016; Roney and Gettler, 2015; Trumble et al., 2015; van Anders et al., 2011; van Anders, 2013), these studies indicate that males who are more androgenic (i.e. who have elevated T in combination with shorter CAGn) may engage in more competition-related and mating-oriented behavior and less empathetic and nurturant behavior.

Given the AR's role in central regulation of testosterone production, and as a moderator of T's target tissue effects, population variation in CAGn could contribute to variation in male life history strategies operating through at least three distinct pathways. First, CAGn could potentially influence T production through the AR receptor's role in negative feedback regulation of the hypothalamic-pituitary-testicular (HPT) axis. T contributes to its own regulation by binding to AR in the brain, reducing hypothalamic release of gonadotropin-hormone releasing hormone (GnRH)(Ryan et al., in press; Tilbrook and Clarke, 2001; Veldhuis et al., 2009). Low levels of GnRH fail to stimulate the production and release of luteinizing hormone (LH) from the pituitary and reduce LH–induced T production in the testes. Due to their more active AR, males with shorter CAGn might be expected to have enhanced negative feedback sensitivity of this pathway to T, thus reducing circulating T. Research on aging and HPT axis function provides preliminary evidence consistent with this model, as men with shorter CAGn have been shown to have lower T and to experience more rapid age-related declines in T production (Crabbe et al., 2007; Krithivas et al., 1999). Although we predict that the direction of the effect will differ from this aging pattern, men with shorter CAGn could have an attenuated decline in T as they transition to new fatherhood because of their greater sensitivity to negative feedback dynamics for the HPT axis. This attenuation effect might be particularly likely in the earlier stages of fatherhood (e.g. the newborn period) when decreases in paternal T appear to be largest, on average (Gettler et al., 2011).

Second, CAGn could modify T's effects and actions in the brain, with implications for cognition and behavior as competitive and sexual opportunities arise, or as men engage with the social demands of partnering and parenting (Carré and Olmstead, 2015; Remage-Healey, 2014). For example, fathers with higher T and shorter CAGn might not engage as empathetically with their young children in the moments when they require patience or sensitivity. Consistent with the genetic component of this hypothesis, a recent neuroimaging study found that fathers with shorter CAGn showed less neural activity in brain areas that facilitate empathy when hearing infant cries (Mascaro et al., 2014). Third, the effects of CAGn on adult male life history could likewise reflect developmental effects of T on neural pathways during early critical periods, such as prenatal and early postnatal life (Alexander, 2014; Auyeung et al., 2009; Berenbaum and Beltz, 2011; Hines, 2011; Kuzawa et al., 2010; Wallen, 2005), adolescence, or young adulthood (Bramen et al., 2012; Peper et al., 2011; Raznahan et al., 2010; Schulz et al., 2009). The developmental effects of high T exposure, when combined with short CAGn, could promote a competition-oriented life history strategy, as has been shown in animal models (Cunningham et al., 2007; Ricci et al., 2009; Schulz et al., 2009).

Although males with a highly androgenic profile are predicted to have poor relationship stability, a number of studies suggest that low T men are at increased risk of depression (reviewed in Ebinger et al., 2009), including among some fathers (Gettler and Oka, 2016). Negative mood and depression contribute to lower quality interactions with partners and children (Ramchandani et al., 2005) and relationship instability (Kessler et al., 1998; Mead, 2002). Because long CAGn is expected to reduce downstream effects of T on the brain and behavior, such a polymorphism could predispose men with low T to depression and negative affect (Harkonen et al., 2003; Sankar and Hampson, 2012; Schneider et al., 2011; Vermeersch et al., 2010; cf. Seidman et al., 2001). These findings suggest that both high and low androgenic extremes could produce similar outcomes for relationship stability and familial interactions, such as paternal caregiving.

Here, we address the possible role of the AR CAG polymorphism as a moderator of the role of T in human male reproductive strategies and life history transitions among participants in a large, longitudinal birth cohort study in the Philippines. We first tested whether CAGn independently predicted partnering and parenting status and fathers' caregiving behaviors. We then build on our past findings at this site (Gettler et al., 2011, 2013, 2015) by testing a series of hypotheses aimed at clarifying the role of CAGn variation in male's mating success, partnering and parenting behavior, and the T response to parenting transitions. We evaluated whether men's CAGn predicted their change in T across the transition to fatherhood, including if CAGn moderated the large decline in Cebuano fathers' T (on average) shortly after the birth of their newborns (Gettler et al., 2011). We hypothesized that men with shorter CAGn would experience an attenuated decline in T as they transitioned to new fatherhood.

We then tested a series of interaction models (CAGn × T) focusing in part on the hypothesis that men at both high and low androgenic extremes would show similar results for relationship instability and fathering behaviors. We hypothesized that men with a high androgenic endocrine-genotypic profile, as indicated by higher T and shorter CAGn, would a) be more likely to experience relationship instability, b) engage in less direct caregiving, and c) have higher reproductive

success. We also tested whether men with low androgenicity, as indicated by longer CAGn and lower T, would be prone to a) relationship instability, b) relatively low direct caregiving as well as c) depressive symptoms.

2. Materials and methods

2.1. Study population

Subjects in this study are participants in the Cebu Longitudinal Health and Nutrition Survey (CLHNS), an ongoing longitudinal population-based birth cohort study of mothers and their infants that began in 1983–84 in Metropolitan Cebu City, Philippines (see Adair et al., 2011). Subjects were interviewed in 2005 and 2009, when they were 21.5 (±0.3, SD) and 26.0 (±0.3) years of age, respectively. This research was conducted under conditions of informed consent with human subject clearance from the Institutional Review Boards of the University of North Carolina at Chapel Hill and Northwestern University.

2.2. Sociodemographics

During in-home visits, CLHNS team members collected socioeconomic, demographic, and behavioral data during interviews conducted in the native language (Cebuano). In this analysis, we classified men who identified themselves as being legally married or cohabitating as "married" (Kuzawa et al., 2009). Divorce is illegal in the Philippines, whereas marital separations and annulments are possible and do occur. We classified men as having experienced "separation" or relationship instability during the 4.5-year follow-up period if they were married multiple times during that specific time period or reported being separated at the follow-up interview. We also categorized men according to whether they had ever experienced separation, based on their marital histories. Single men were those who reported being unmarried.

In the 2005 CLHNS data collection, men reported their household composition, including the presence of their children, but did not report whether they had children who were not residing with them. We therefore also defined men as fathers if they reported (in 2009) having biological children in 2005 but did not report living with their child in the 2005 interview and reported having impregnated a woman in the past (in 2005). In 2009, men reported whether they were fathers, the children's ages, and their biological relatedness to their children. For the purposes of these analyses, we classified men as fathers if they reported having biological children (adapted from Gettler et al., 2011; Gettler et al., 2015). For fathers at follow-up, we also categorized them according to whether their youngest child was a: newborn (1 month old or less), infant (1 year old or younger but older than 1 month), or older child (older than 1 year)(Gettler et al., 2011). Subjects also reported their employment status, educational attainment, and their religiosity (whether they considered themselves religious or not).

2.3. Health

Subjects reported their total sleep time and general health (poor, good or excellent). They also reported their psychosocial stress in the month preceding sample collection, via a modified version of the 10-item Perceived Stress Scale (PSS) (Cohen et al., 1983). Similarly, they indicated whether they had experienced 16 depression-related somatic symptoms and feelings/emotions (none of the time, occasionally, or most of the time) in the past four weeks. We used Cronbach's alpha analyses and Stata's "item detail" command to assess the internal consistency of the scale. We eliminated four items that reduced the scale's reliability. The resulting 12-item scale had a Cronbach's alpha = 0.75 and mirrors a prior analysis of both male and female subjects enrolled in the CLHNS using the same 12 depression-related symptoms (Hindin and Gultiano, 2006). We provide the full 16-item scale in the supplemental material and identify the four items that were eliminated. These depression symptom data were only collected at the baseline interview.

2.4. Extra-pair sexual behavior

At follow-up, men reported whether they had been in a serious relationship in the past 12 months and the frequency with which they had intercourse with someone who was not their current committed partner in the preceding 12 months. To ensure the accuracy of the variable, we only identified individuals as engaging in extra-pair sexual activity if they had been in a relationship for 12 months or more (Gettler et al., 2013). These data were only collected at follow-up.

2.5. Paternal care

In 2009, we measured fathers' caregiving through two different approaches. Fathers reported their *routine* involvement in direct care in response to the question, "How much time do you usually spend providing physical care to your children on a daily basis?" with men grouping themselves according to the following categories: no contact/0 min, less than an hour, 1 to 3 h, and 3+ hours. Because there were relatively few men in the lowest two care levels, we grouped them into a single low care group denoting <1 h spent daily in direct care (Gettler et al., 2013). Fathers also reported the *recent* amount of time (in hours and minutes) they had allocated in the past week to a list of 20 paternal caregiving behaviors informed by a large-scale survey on fathering and caregiving in the Philippines. Examples included feeding children, playing, bathing children, reading to children, putting children to sleep, and walking children to school (adapted from Gettler et al., 2011; Gettler et al., 2015). We analyzed this "recent care" variable as total minutes of care.

2.6. Salivary T collection and measurement

In both 2005 and 2009, participants were each given instructions and two polypropylene tubes for saliva collection. They were asked to collect the first sample immediately before bed (PM), with mean sampling times of 10:41 PM ± 2:40 (SD) in 2005 and 10:23 PM ± 2:25 in 2009. They then collected the second sample immediately on waking the following morning (AM) and reported the time of collection. Mean AM sampling times were 6:49 AM ± 2:01 in 2005 and 6:54 AM ± 1:51 in 2009. These samples were shipped on dry ice to Northwestern University, where they were stored at −80 °C. T concentrations were determined at the Laboratory for Human Biology Research at Northwestern University using an enzyme immunoassay protocol developed for use with saliva samples (Salimetrics, State College, PA; Kit No. 1-2402). Interassay coefficients of variation were 13.7% and 11.5% for high (200 pg/ml) and low (20 pg/ml) kit-based control samples, respectively, in 2005 samples and 7.8% and 17.9% for high and low control samples, respectively, in 2009 samples. Two men were eliminated from these analyses on the basis of T values that were 6+ SD above the mean, indicating potential blood contamination.

2.7. Androgen receptor CAGn measurement

2.7.1. Genotyping

DNA samples were run at Dr. Geoff Hayes's laboratory at Northwestern University on 384-well microtiter plates. For quality control, we randomly placed three Centre d'Etude du Polymorphisme Humain (CEPH) control DNA samples, isolated from lymphoblast cell lines, in each quadrant of the 384-well plates. The CAGn repeat in the androgen receptor (AR) gene was amplified using a previous protocol (Ackerman et al., 2010, 2012), with fluorescently labeled primers (AR CAGn forward, 5′-NED-GTGCGCGAAGTGATCCAGAA-3′; and reverse, 5′-TAGCCTGTGGGGCCTCTACG-3′.) For each PCR, 20 ng of genomic DNA

was amplified in a total volume of 8 μl in the presence of 200 μm deoxynucleotide triphosphate, 1.5 mm MgCl2, 0.7 U AmpliTaq polymerase, and 0.75 μm of forward primer and 0.75 μm of reverse primer. PCR products were electrophoresed in the presence of an internal size standard (GeneScan 500 ROX) at room temperature on the Applied Biosystems 3130XL Capillary DNA sequence analysis system, and genotypes were assigned using the GENEMAPPER software version 4.0 (Applied Biosystems). We also visually examined the chromatogram for each sample to confirm the genotype assignment.

2.7.2. Quality control

853 males were genotyped along with 323 female relatives. Of these 1176 typed individuals, 18 samples had ambiguous genotyping calls that were not clearly consistent with three base pair repeats (e.g. an allele which was in between a 31 and 32 in size) and were excluded. 41 samples had quality control replicates that the individual running laboratory analyses and determining genotyping calls was blinded to. All of these 41 quality control replicate pairs matched. One of the 853 male individuals showed a second AR allele and was dropped since males are only expected to show one allele on the AR locus located on the X chromosome. This heterozygous male likely represents sample contamination or mix-up, but we note that copy-number variant (CNV) gains have been observed at the AR locus in healthy individuals, which could also explain this result (Database of Genomic Variants, http://dgv.tcag.ca/, accessed on July 11, 2014). In the broader analyses that included mothers and these male offspring, 176 of 177 (99.4%) of mother-offspring pairs contained at least one matching allele. The single mother-offspring pair without the expected matching allele was dropped from the analysis. We excluded one subject with AR CAGn = 45 (Ryan et al., in press).

2.8. Statistical analyses

We conducted analyses using version 14.0 of Stata (Stata Corporation, College Station, TX). We analyzed T (pg/mL), AR CAGn, number of children, educational attainment, total sleep time, psychosocial stress scores, depression symptom scores, and fathers' prior week's caregiving time as continuous variables. We adjusted AM and PM T for their sampling times prior to our analyses. We used those time-adjusted T values to calculate absolute change in T (ΔT) between baseline (2005) and follow-up (2009) (Gettler et al., 2012). See Gettler et al. (2013) for our rationale for using absolute ΔT for CLHNS analyses.

We first tested whether CAGn predicted men's marital and fatherhood status (logistic regression) as well as their number of children (negative binomial regression) at follow-up. We predicted fathers' involvement in caregiving at follow-up from their CAGn, using multinomial logistic regression for the categorical variable (routine involvement in direct care) and zero-inflated negative binomial regression for the continuous variable (prior week's minutes of care). In all of our models, tests of model fit indicated that zero-inflated negative binomial regression was a better fit for these recent (prior week's) caregiving data than either a zero-inflated poisson model or an ordinary negative binomial regression.

We then we used OLS regression to predict ΔT from CAGn for men who transitioned from being non-fathers (baseline) to fathers (follow-up). Among these new fathers, we also tested whether CAGn moderated the relationship between the age of the man's youngest child and ΔT (Gettler et al., 2011). Next, we conducted a series of analyses to test whether CAGn moderated relationships between T, life history outcomes, and paternal behavior. Using logistic regression, we tested whether (baseline T × CAGn) interactions predicted whether men had experienced marital separation over the 4.5-year follow-up period. We also assessed cross-sectional relationships between (T × CAGn) interactions and caregiving for all men who were fathers at follow-up and predicted new fathers' caregiving (follow-up) from their pre-fatherhood androgenicity (baseline T × CAGn) interactions. Finally, building

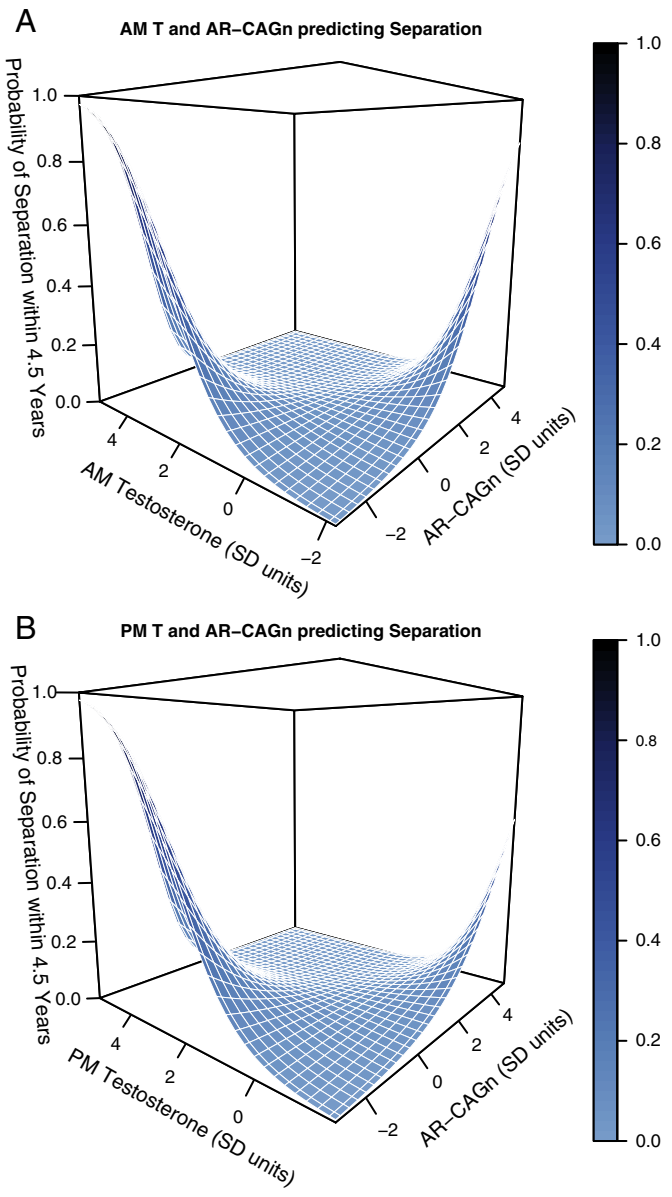

Fig. 1. a-b. Men's predicted probabilities of having experienced relationship instability (separation) over the 4.5-year study period based on androgenicity (CAGn × baseline testosterone [T]). Men had higher probabilities of experiencing relationship instability between baseline (age 21.5 ± 0.3 years) and follow-up (age 26.0 ± 0.3 years) if their androgenicity was higher (i.e. shorter CAGn and higher T) or lower (i.e. longer CAGn and lower T). The (CAGn × T) interaction terms were significant ($p < 0.05$) for both waking (AM) and evening (PM) baseline T. See Tables 2 and 3 for the full model results.

from prior analyses (Gettler et al., 2011), we used logistic regression to test whether (baseline T × CAGn) interactions predicted non-fathers' (baseline) likelihood of becoming fathers by follow-up and single non-fathers likelihood of becoming married by follow-up. Using negative binomial regression, we also predicted non-fathers' number of children from (baseline T × CAGn) interactions. For each set of analyses, we ran an initial model without covariates and a second model in which we added sociodemographic and health-related variables that we hypothesized could have confounded, masked, or mediated associations between the dependent variables and androgenicity. While we carefully selected covariates for each set of analyses, the full battery of combined covariates across all analyses includes: marital status and separation history, number of children, education, employment status, religiosity, depression symptoms, psychosocial stress, general health, and total sleep time. As these analyses aimed (in part) at identifying relevant

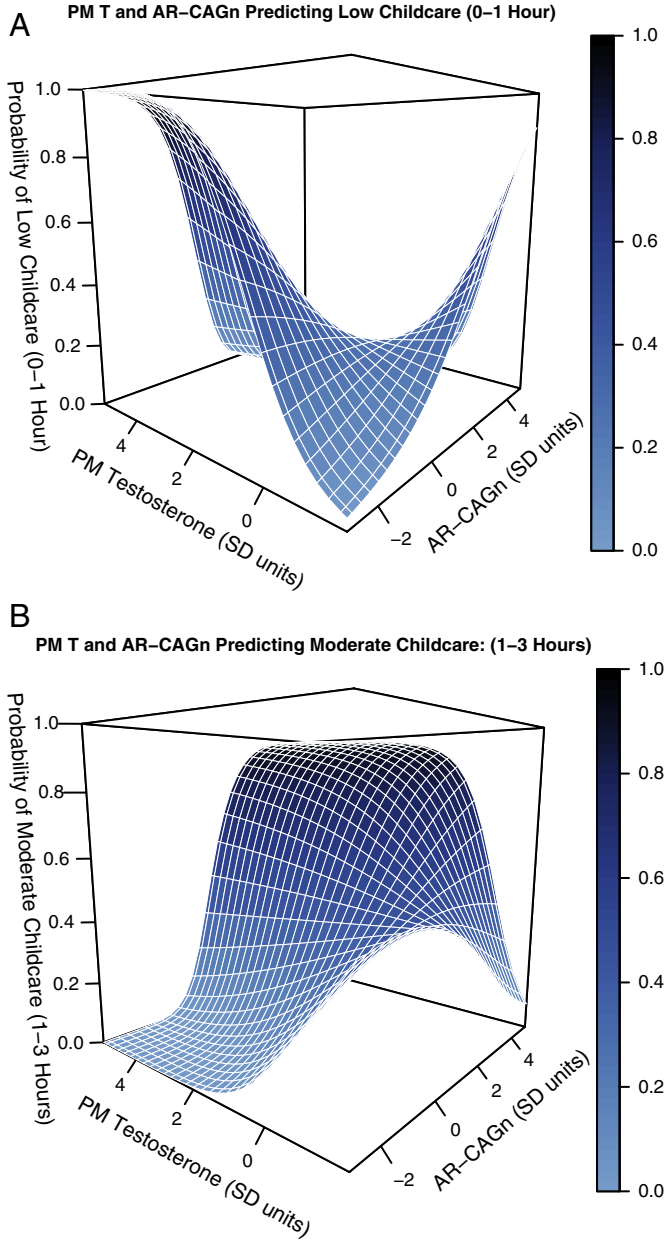

Fig. 2. a-b. Men's predicted probabilities of being a father who engages in low direct child care (Fig. 2a) versus a father who engages in moderate direct care (Fig. 2b) at follow-up, based on androgenicity (CAGn × baseline evening testosterone [T]). These analyses focus on men who were non-fathers at baseline, thus they model how pre-fatherhood androgenicity predicts men's paternal care 4.5-years later, after the transition to parenthood. Men had higher probabilities of being fathers who engaged in low levels of direct care at follow-up (age 26.0 ± 0.3 years) if their androgenicity was higher (i.e. shorter CAGn and elevated evening T) or lower (i.e. longer CAGn and reduced evening T) at baseline (age 21.5 ± 0.3 years) ($p = 0.020$). See Table 5 for the full model results.

pathways, we also tested whether androgenicity was predictive of men's depression scores (negative binomial regression) and infidelity (logistic regression). We also tested whether depression scores and infidelity, respectively, were related to men's history of separation and paternal caregiving (depression symptoms only). In R, we created Figs. 1 and 2 using the "plot3D" package (R Core Development Team, 2011; Soetaert, 2016), while we created Supplemental Fig. 1 following predictive margins in Stata. In the text of the Results, we also report results from predictive margins in Stata to help convey the effect sizes for the models. For those predictive margins analyses, we defined males as having: "higher androgenicity" (+1 SD for T, −1 SD for CAGn), "lower androgenicity" (−1 SD for T, +1 SD for CAGn), or "moderate androgenicity" ([+1 SD for T, +1 SD for CAGn] or [−1 SD for T, −1 SD for CAGn]). We evaluated statistical significance at $p < 0.05$.

3. Results

Table 1 presents sociodemographic, behavioral, health, and biological characteristics of the full sample, and also stratified on a median split of CAGn for descriptive purposes. As we have shown previously (Gettler et al., 2011), men's T declined modestly, on average, over the 4.5-year follow-up period. The mean CAGn for the sample was 21.04 (±3.41 SD), ranging from 11 to 38, which is similar to other Asian populations (Ryan et al., in press). The sociodemographic, behavioral, and biological data in Table 1 did not vary based on a comparison of men with shorter versus longer CAGn, with the exception of employment status. Men above the median for CAGn were less likely to be employed than men below the median ($p = 0.037$). At baseline, the majority of men (>90%) reported being in good or excellent health. Roughly half the sample had transitioned to fatherhood by follow up at age 26.0 years and a large percentage of fathers (>70%) reported being either moderately or highly involved in daily childcare.

In unadjusted bivariate analyses, CAGn was not predictive of men's likelihood of being separated or married at follow-up (both $p > 0.5$). Similarly, CAGn did not predict men's likelihood of being a father at follow-up ($p > 0.8$) or their number of children ($p > 0.4$). In addition, we did not find that fathers' CAGn was predictive of either of our paternal care measures (all $p \geq 0.2$). Finally, similar to our prior results in Ryan et al. (in press), CAGn and T (at any time point in the study) were not significantly correlated (all $p > 0.1$).

Hypothesis 1. Men with shorter CAGn will have a lesser decline in T as they transition to fatherhood.

First, we tested whether men's CAGn was predictive of their ΔT as they transitioned from being non-fathers at baseline to being fathers at follow-up ($n = 230$). CAGn was not predictive of men's change in AM or PM T as they transitioned to fatherhood (both $p > 0.5$). Building from our prior research (Gettler et al., 2011), we hypothesized that men with shorter CAGn would experience a lesser decline in T near the birth of their children, due to their increased AR sensitivity. Thus, we tested for a moderating effect of youngest child's age on the relationship between CAGn and ΔT. We did not find support for this hypothesis ($p > 0.2$ for all interaction terms; Supp. Table 1), as men's ΔT did not differ based upon the interaction between their CAGn and whether they were a parent to a newborn, infant, or older child.

Hypothesis 2. Men with higher T + shorter CAGn *or* lower T + longer CAGn will be more likely to experience unstable relationships.

We next tested whether (CAGn × baseline T) predicted men's likelihood of being separated during the 4.5-year follow-up period ($n = 683$). Consistent with our hypotheses, men with shorter CAGn were more likely to have been separated by follow-up if their baseline AM T was high and less likely if their baseline AM T was low (CAGn × baseline AM T interaction term, $p = 0.004$; Fig. 1a; Table 2). The opposite was true for men with longer CAGn, who were more likely to have been separated by follow-up with low baseline AM T and less likely with high baseline AM T. Based on predictive margins, males with higher AM androgenicity (7%) or lower AM androgenicity (6%) had higher probabilities of separation than males with more moderate AM androgenicity (2–3%) (see the Materials and methods for our definitions of lower, moderate, and higher androgenicity in these effect size statements).

The (CAGn × baseline PM T) interaction term was also significant ($p = 0.041$) and the results mirrored the patterns from the AM T interaction, with those men with elevated baseline PM T and shorter CAGn having the highest probability of separation by follow-up (see Fig. 1b; Table 3). Based on predictive margins, males with higher PM androgenicity (9%) or lower PM androgenicity (7%) had higher

Table 1
Sample characteristics stratified on low and high AR CAGn repeat length (n = 683).

	All(n = 683) Mean ± s.d.	Low CAGn[a] (n = 420) Mean ± s.d	High CAGn[a] (n = 263) Mean ± s.d	p value
Sociodemographic characteristics[b]				
Age at baseline (years)	21.48 ± 0.30	21.49 ± 0.29	21.47 ± 0.30	0.439
Age at follow-up (years)[c]	25.96 ± 0.31	25.96 ± 0.31	25.96 ± 0.30	0.973
Highest grade completed	9.84 ± 3.12	9.95 ± 3.09	9.66 ± 3.16	0.244
Employment status (% working)	57.8	61.0	52.9	0.037
Religiosity (% who are religious)	66.5	66.2	66.9	0.844
General health status				
Poor	6.9	7.6	5.7	0.609
Good	80.0	79.1	81.4	0.609
Excellent	13.2	13.3	12.9	0.609
Depression symptoms score	4.34 ± 2.97	4.39 ± 3.04	4.27 ± 2.84	0.613
Relationship characteristics[d]				
Married 2005	18.5	18.1	19.0	0.764
Married 2009[c]	53.3	52.8	54.2	0.714
Separated between 2005 and 2009	6.2	6.2	6.1	0.955
Infidelity in past 12 months (follow-up)[e]	5.1	4.6	6.1	0.451
Fatherhood characteristics				
Father 2005	14.8	14.5	15.2	0.806
Father 2009[c]	50.1	49.9	50.6	0.864
Number of children (follow-up)[f]	1.60 ± 0.82	1.58 ± 0.75	1.63 ± 0.93	0.936
Age of oldest child (follow-up) (years)[f]	3.24 ± 2.18	3.24 ± 2.18	3.24 ± 2.19	0.978
Hours of recent caregiving (follow-up)[f]	24.88 ± 32.19	24.87 ± 32.37	24.90 ± 32.02	0.827
Routine caregiving (follow-up)[f]				
≤1 h of care	27.0	27.7	25.9	0.221
1–3 h of care	43.5	40.2	48.9	0.221
3+ hours of care	29.5	32.1	25.2	0.221
Physiological variables				
AR CAGn	21.04 ± 3.41	19.14 ± 2.32	24.08 ± 2.57	0.0001
Testosterone values				
AM T 2005 (pg/ml)	192.20 ± 75.81	191.78 ± 77.26	192.88 ± 73.58	0.854
AM T 2009 (pg/ml)[c]	162.61 ± 61.18	160.63 ± 60.87	165.85 ± 61.67	0.266
PM T 2005 (pg/ml)	118.41 ± 52.29	117.70 ± 53.70	119.54 ± 50.02	0.656
PM T 2009 (pg/ml)[c]	95.01 ± 42.83	93.19 ± 44.05	97.97 ± 40.67	0.145

[a] Test for significant differences by median split of the androgen receptor polyglutamine repeat length (AR CAGn) (low CAGn ≤ 21 < high CAGn); unpaired, two-tailed *t*-test, chi-square, or Mann-Whitney *U* test. The median split of subjects is uneven because of the high number of men with the median value (CAGn = 21), who are included in the "low" category.
[b] All the sociodemographic data reported here are from the baseline survey in 2005 unless otherwise noted.
[c] n = 724.
[d] Married: legally married or cohabitating.
[e] n = 506.
[f] Restricted to fathers in 2009 (n = 363); age of oldest child (n = 355). P values for routine caregiving reflect a single chi-square test.

probabilities of separation than males with more moderate PM androgenicity (4%). The results for both AM T ($p = 0.002$) and PM T ($p = 0.046$) remained significant and virtually unchanged after controlling for sociodemographic and health covariates that might confound or mask associations between baseline androgenicity and later separation (Tables 2-3).

For an eligible sub-sample of men (n = 506), we then tested whether highly androgenic men (follow-up) reported greater extra-pair intercourse in the past year (at follow-up), as we hypothesized that infidelity could be in the pathway between higher androgenicity and relationship instability at Cebu. We did not find support for this hypothesis, as androgenicity was not related to reports of infidelity (CAGn × follow-up T interaction terms both $p > 0.3$). However, there was an association between men having experienced separation in the past and their having engaged in infidelity (n = 594; Fisher's exact, $p = 0.002$). Among men who had experienced separation by follow-up, 16% reported recent infidelity, whereas only 4% of other men did so.

Finally, while we found support for our hypothesis that men with low androgenicity would have an elevated likelihood of separation by follow-up, our results do not indicate that this is mediated by heightened risk of depression. Men with higher depression scores at baseline were not more likely to become separated over the follow-up period ($p > 0.2$) and controlling for depression scores did not affect the relationship between androgenicity and separation (Tables 2-3). In addition, men's androgenicity (CAGn × baseline T) did not significantly predict their total depression score (AM and PM T interaction terms both $p > 0.1$).

Hypothesis 3. Men with higher T + shorter CAGn *or* lower T + longer CAGn will be less likely to engage in direct caregiving.

3.1. Cross-sectional models for all fathers in 2009

Drawing on all men who were fathers at follow-up (n = 363), we tested for cross-sectional relationships between men's (CAGn × follow-up T) and their paternal care. For both AM and PM T, the interaction terms for (CAGn × T) were not significant predictors of fathers' care in the prior week at follow-up (both $p > 0.3$). For routine care, fathers who had lower CAGn and higher AM T at baseline tended to provide minimal care (0–1 h per day) and less commonly reported moderate care (1–3 h per day)(CAGn × follow-up AM T interaction term, $p = 0.007$) which remained significant after we added covariates to the model ($p = 0.010$; Supp. Table 2). The interaction term comparing men's likelihood of providing minimal care versus extensive care (3+ hours per day) was not significant ($p = 0.166$). For evening T, the interaction (CAGn × follow-up PM T) was not a significant predictor of fathers' routine care (both interaction terms $p > 0.5$).

3.2. Longitudinal models for men who were non-fathers in 2005 and transitioned to fatherhood by 2009

Using the sub-sample of men who were non-fathers at baseline (age 21.5 years; n = 237), we found a significant interaction between baseline AM T and CAGn in predicting men's care in the prior week at follow-

Table 2
Predicting men's likelihood of separation (follow-up) from CAGn × baseline waking T[a].

	Model 1			Model 2		
	OR	95% CI	p	OR	95% CI	p
Main effects						
Waking T	0.97	(0.71, 1.32)	0.834	1.00	(0.71, 1.40)	0.980
CAGn	0.98	(0.71, 1.37)	0.923	0.92	(0.65, 1.30)	0.637
Interaction term						
CAGn × waking T	0.65	(0.49, 0.87)	0.004	0.61	(0.44, 0.83)	0.002
Covariates[b]						
Married				7.96	(3.09, 20.48)	0.0001
Father				0.32	(0.11, 0.94)	0.037
Education (highest grade)				0.92	(0.83, 1.02)	0.116
Religious				1.88	(0.85, 4.15)	0.119
Employed				1.18	(0.56, 2.51)	0.662
Psychosocial stress				0.99	(0.91, 1.07)	0.775
General health						
Good				0.45	(0.15, 1.34)	0.154
Excellent				0.14	(0.02, 0.85)	0.033
Depression symptoms score				1.03	(0.93, 1.15)	0.546
Model LR chi-square(df)	LR chi2(3): 8.30; p = 0.040			LR chi2(12): 42.36; p < 0.0001		

[a] n = 683. We converted testosterone (T) and CAGn to z-scores. Covariates are from the baseline (2005) survey.
[b] Excluded comparisons for categorical covariates: -non-married men. -non-fathers. -men who did not consider themselves religious. -unemployed men. -men who self-reported their health as poor. -non-married men. -non-fathers.

up. Non-fathers with shorter CAGn were involved caregivers at follow-up if their baseline T was low but performed little care if their T was high (CAGn × baseline AM T interaction term, p = 0.006; Supp. Fig. 1; Table 4). We observed the opposite pattern for men with longer CAGn, who were more involved at follow-up if their baseline T was high and less involved when it was low. These results were largely unchanged with the addition of covariates (p = 0.012; Table 4). Using predictive margins, we found that fathers with lower AM androgenicity were predicted to engage in ~16 h of weekly care (950 min). Men with higher AM androgenicity were predicted to perform ~26 h of care per week (1547 min). The predicted care values for fathers with more moderate AM androgenicity were ~31 h (1860–1868 min).

Table 3
predicting men's likelihood of separation (follow-up) from CAGn × baseline evening T[a].

	Model 1			Model 2		
	OR	95% CI	p	OR	95% CI	p
Main effects						
Evening T	1.11	(0.81, 1.51)	0.525	1.14	(0.82, 1.59)	0.443
CAGn	0.97	(0.70, 1.35)	0.866	0.89	(0.64, 1.23)	0.473
Interaction term						
CAGn × evening T	0.69	(0.48, 0.99)	0.041	0.67	(0.46, 0.99)	0.046
Covariates[b]						
Married				7.16	(2.81, 18.24)	0.0001
Father				0.35	(0.12, 1.03)	0.056
Education (highest grade)				0.93	(0.84, 1.03)	0.160
Religious				1.71	(0.78, 3.73)	0.177
Employed				1.26	(0.60, 2.66)	0.536
Psychosocial stress				0.99	(0.91, 1.07)	0.715
General health						
Good				0.51	(0.17, 1.49)	0.218
Excellent				0.16	(0.03, 0.92)	0.040
Depression symptoms score				1.04	(0.93, 1.16)	0.456
Model LR chi-square(df)	LR chi2(3): 5.51; p = 0.138			LR chi2(12): 37.61; p = 0.0002		

[a] n = 683. We converted testosterone (T) and CAGn to z-scores. Covariates are from the baseline (2005) survey.
[b] Excluded comparisons for categorical covariates: -non-married men. -non-fathers. -men who did not consider themselves religious. -unemployed men. -men who self-reported their health as poor.

The interaction term for (CAGn × baseline PM T) approached significance (p = 0.055) and the p value increased with the addition of covariates to the model (p = 0.113). The direction of the results was generally similar to the AM T model (Supp. Fig. 1; Supp. Table 3). Predictive margins showed that fathers with lower PM androgenicity were predicted to perform ~19 h of care per week (1159 min). Higher PM androgenicity fathers were predicted to engage in ~22 h of weekly care (1334 min). Finally, the predicted care values for fathers with more moderate PM androgenicity were ~28–32 h (1687–1897 min).

Testing similar models for routine care, non-fathers who had lower CAGn and higher PM T at baseline tended to provide minimal care (0–1 h per day) and less commonly reported moderate care (1–3 h per day) as fathers at follow-up (CAGn × baseline PM T interaction term, p = 0.020; Fig. 2a-b; Table 5). Non-fathers who had longer CAGn and higher PM T at baseline were unlikely to provide minimal care (0–1 h per day) whereas they more commonly engaged in moderate care (1–3 h per day)(Fig. 2a-b). The effect size modestly increased when we added covariates to this model (p = 0.019; Table 5). Based on predictive margins, men with lower PM androgenicity (31%) and higher PM androgenicity (47%) had elevated probabilities of providing minimal care, compared to men with moderate PM androgenicity (20%). Meanwhile, men with more intermediate PM androgenicity had greater probabilities of engaging in moderate caregiving (39–52%), especially compared to those with higher PM androgenicity (18%). The (CAGn × PM T) interaction term comparing men's likelihood of providing minimal care compared to extensive care (3+ hours per day) initially approached significance (p = 0.088), but it was non-significant in the full model (p = 0.175).

For waking T, the interaction (CAGn × baseline AM T) was not a significant predictor of new fathers' likelihood of minimal vs. moderate care (p = 0.130) but the direction of the results was generally similar to the PM T interaction. The interaction term for extensive care was also not significant (p = 0.368).

Although we found support for our hypothesis that men with low androgenicity would tend to be minimally involved with caregiving, this result was not mediated by depressive symptoms. Men with higher depression scores at baseline did not have a stronger likelihood of being uninvolved fathers at follow-up (all p > 0.2) and controlling for depression scores did not affect the relationship between androgenicity and paternal caregiving (Tables 4-5; Supp. Table 3).

Hypothesis 4. Elevated T and shorter CAGn among young adults will relate to higher reproductive success.

Contrary to our hypotheses, we did not find that interactions between CAGn and baseline AM or PM T predicted non-fathers' likelihood of being fathers by follow-up (n = 579; both p > 0.2; Supp. Table 4). Similarly, the interactions between CAGn and AM and PM T did not predict their number of children at follow-up (both p > 0.3; Supp. Table 4). Expanding on our prior, related analyses (Gettler et al., 2011), we also predicted single non-fathers' likelihood of being married or married fathers by follow-up based on baseline T × CAGn interactions, but found no significant results (all p > 0.4).

4. Discussion

Drawing on a large longitudinal study in the Philippines, we tested a series of hypotheses linking variation in an androgen receptor genetic polymorphism (AR CAGn), T, life history transitions, and nurturant behavior (paternal caregiving) in young adult men. Our findings are consistent with the notion that variability in AR CAGn contributes to between-male variation in evolutionarily-relevant life history domains,

Table 4
predicting recent caregiving (follow-up) for men who were non-fathers at baseline from CAGn × baseline waking T[a].

	Model 1			Model 2		
	IRR	95% CI	p	IRR	95% CI	p
Main effects						
Waking T	1.13	(0.97, 1.32)	0.111	1.10	(0.95, 1.28)	0.213
CAGn	0.89	(0.75, 1.04)	0.143	0.89	(0.76, 1.05)	0.171
Interaction term						
CAGn × waking T	1.24	(1.06, 1.44)	0.006	1.21	(1.04, 1.41)	0.012
Covariates[b]						
Married				0.79	(0.51, 1.22)	0.286
Marital separation				0.80	(0.47, 1.37)	0.423
Education (highest grade)				0.98	(0.94, 1.03)	0.534
Religious				1.12	(0.83, 1.52)	0.464
Employed				0.74	(0.55, 0.99)	0.044
Psychosocial stress				1.00	(0.97, 1.04)	0.895
General health						
Good				0.85	(0.46, 1.57)	0.608
Excellent				0.62	(0.30, 1.26)	0.187
Depression symptoms score				0.99	(0.95, 1.04)	0.813
Model LR chi-square(df)	LR chi2(3): 10.52; p = 0.015			LR chi2(24): 19.31; p = 0.081		

[a] n = 237. IRR: incident rate ratio. Recent caregiving at follow-up: fathers reported the amount of time (in hours and minutes) they had allocated in the past week to a list of 20 paternal caregiving behaviors. Covariates are from the baseline (2005) survey. Marital separation also includes 2009 data.
[b] Excluded comparisons for categorical covariates: -non-married men. -men who had not experienced marital separation at baseline or by follow-up. -men who did not consider themselves religious. -unemployed men. -men who self-reported their health as poor.

such as relationship stability and paternal investment. Although specific findings varied by analysis, the general pattern across outcomes is one in which the extremes of high or low androgenicity, as reflected in combinations of higher T-shorter CAGn or lower T-longer CAGn, predicted lower paternal caregiving and reduced relationship stability through time. Evidence for invested fathering and relationship stability at intermediate levels of androgenicity is potentially consistent with a contributing role of balancing selection in shaping CAGn variation and HPT regulation (Ryan and Crespi, 2012).

Table 5
predicting routine caregiving (follow-up) for men who were non-fathers at baseline from CAGn × baseline evening T[a].

	Model 1			Model 2		
	RRR	95% CI	p	RRR	95% CI	p
Main effects						
Evening T	0.76	(0.55, 1.05)	0.096	0.73	(0.52, 1.03)	0.074
CAGn	1.50	(1.04, 2.16)	0.028	1.57	(1.04, 2.36)	0.031
Interaction term						
CAGn × evening T	1.75	(1.09, 2.80)	0.020	1.87	(1.11, 3.15)	0.019
Covariates[b]						
Married				1.12	(0.41, 3.06)	0.822
Marital separation				0.37	(0.14, 0.99)	0.049
Education (highest grade)				1.00	(0.88, 1.14)	0.997
Religious				0.97	(0.46, 2.05)	0.942
Employed				0.98	(0.47, 2.04)	0.951
Psychosocial stress				1.06	(0.98, 1.14)	0.165
General health						
Good				3.86	(0.70, 21.37)	0.122
Excellent				7.48	(1.07, 52.44)	0.043
Depression symptom scores				0.94	(0.84, 1.05)	0.292
Model LR chi-square(df)	LR chi2(6): 18.29; p = 0.006			LR chi2(24): 56.60; p = 0.0002		

[a] n = 237. Relative risk ratios (RRR) reflect the likelihood of fathers reporting moderate (1–3 h of daily care) versus the low care comparison category (<1 h). Routine caregiving at follow-up: Fathers categorically reported their routine involvement in direct care in response to the question, "How much time do you usually spend providing physical care to your children on a daily basis?" (see Materials and methods). Covariates are from the baseline (2005) survey. Marital separation also includes 2009 data.
[b] Excluded comparisons for categorical covariates: -non-married men. -men who had not experienced marital separation at baseline or by follow-up. -men who did not consider themselves religious. -unemployed men. -men who self-reported their health as poor (baseline).

The HPT axis operates as a negative feedback loop, with T binding to AR in the brain to influence its own regulation (Tilbrook and Clarke, 2001; Veldhuis et al., 2009). We hypothesized that through these feedback loop dynamics CAGn variation could contribute to differential T responses (across men) to the transition to fatherhood. We have thoroughly documented that T declines as the men in this sample transition to partnering and parenthood (Gettler et al., 2011, 2012, 2013, 2015), with decreases in T being largest during the earliest weeks of fatherhood (Gettler et al., 2011). Evidence for lower luteinizing hormone (LH) among fathers in this sample suggests that downregulation of married fathers' T likely originates upstream of the testes at the level of the brain and pituitary (Kuzawa et al., 2009). Here, we did not find that CAGn moderated those changes in T, and a recent study in this population also found little evidence for a role of CAGn in systemic regulation of T (Ryan et al., in press). It remains unclear how a recalibration of HPT axis set points in response to partnering and fatherhood occurs and how variation in that recalibration between-men emerges (Gettler, 2014, 2016). Although the details remain to be explored, past work in humans and other species point to a likely role of genetic, epigenetic, and other physiological differences (e.g. shifts in receptor densities) as well as neural reorganization (as occurs in some animal fathers [Kozorovitskiy et al., 2006]), which cumulatively impact GnRH regulation in the brain (Gettler, 2014, 2016).

We found support for the hypothesis that highly androgenic men would experience more instability in long-term partnerships. Men who were highly androgenic (baseline) were subsequently more likely to be separated by follow-up or to have been married multiple times during the 4.5-year study period. Our findings are consistent with two large prior studies of U.S. servicemen that found that married men with elevated T were more likely to become divorced, through time (Mazur and Michalek, 1998), or to have been divorced (Booth and Dabbs, 1993). To our knowledge, CAGn was not measured in these prior studies. More recent U.S-based studies have also shown that men and women with lower T report greater relationship commitment and satisfaction (Edelstein et al., 2014), and males with reduced T express less interest in extra-pair romantic or sexual opportunities (McIntyre et al., 2006; Puts et al., 2015; van Anders and Goldey, 2010). While we have limited information to explore pathways through

which this relationship disruption emerged for highly androgenic men at Cebu, past research points to several plausible possibilities.

Men with elevated T (particularly when combined with shorter CAGn) might be prone to anger, attentive to social threat and status or power challenges, and inclined towards reactive aggression (Carré and Olmstead, 2015; Manuck et al., 2010). Collectively, such dispositions could contribute to day-to-day relationship conflict (e.g. bickering, arguing) and more extreme forms of verbal and physical aggression towards partners (Booth and Dabbs, 1993). Prior research suggests that men with high T also exhibit tendencies towards alcohol over-use and other vices (Booth and Dabbs, 1993; Dabbs and Morris, 1990). Individually or in combination, all of these factors could influence women's desires and decisions to separate from their partners. Similarly, highly androgenic men might also engage in greater infidelity, as it is not uncommon for men to have mistresses in the Philippines (Gonzales et al., 2004; Lacar, 1993; McCann-Erickson, 1995 in Gonzales et al., 2004). We did not find evidence for this in our data. Our null findings are potentially consistent with a recently proposed psychobiological framework but could also be due to data limitations.

Expanding from results of a U.S.-based study and prior psychobiological data, Puts et al. (2015) recently proposed that elevated T heightens men's sociosexual psychology (e.g. desires for uncommitted sexual partners) but that when their sociosexual behavior meets those psychological expectations, they will experience downregulated T. Hence, in their model there is an ongoing feedback between T, sociosexual psychology, and sociosexual behavior (Puts et al., 2015). Based on this framework, in our study, some males who engaged in infidelity in the prior year could have had downregulated T (hence lower androgenicity) at the time of data collection, which would diminish the relationship between current androgenicity and recent infidelity. In Cebu, men with a history of separation were more likely to have been unfaithful to their present partner. That is consistent with the idea that there are commonalities between men's propensities towards infidelity and relationship dissolution or instability, the latter of which is predicted by higher androgenicity at this site.

However, we also acknowledge that speculation on null associations can be problematic, and it is important to note that the variables we used were not designed to assess androgenicity-infidelity linkages. Moreover, extra-pair sexual behavior may be difficult to discern through self-report measures, particularly in a conservative cultural setting such as Cebu. In addition, we were only able to test whether androgenicity was linked to men's infidelity in the past 12 months outside of an ongoing (12-month or more) relationship. In total, our measures likely underestimate the true rate of infidelity. We hope to more thoroughly address these types of questions in future surveys at this site.

We also found support for the hypothesis that men with particularly low androgenicity (low T, longer CAGn) would be more likely to experience relationship instability. Past research indicates that males with low androgenicity show tendencies towards negative mood and depressive symptoms (Ebinger et al., 2009; Harkonen et al., 2003; Sankar and Hampson, 2012; Schneider et al., 2011; Vermeersch et al., 2010), with some evidence for a curvilinear relationship that also implicates higher T as a depression risk factor (Booth et al., 1999). Such mood states and mental health concerns can both contribute to and result from marital conflict and distress (Kessler et al., 1998; Mead, 2002). In the present analysis, we did not find that men at either the higher or lower ends of androgenicity reported greater total depressive symptoms during the baseline data collection. This suggests that the increased tendency towards separation among low androgenic men emerged through a different pathway. While speculative, an alternative possibility is that men with lower androgenicity may be prone to negative mood or lower resilience when challenging circumstances or hardships arise (Charney, 2004; Russo et al., 2012), such as after once marital conflict emerges, contributing to their elevated prevalence of separation. In such a scenario, women might specifically de-invest in the partnership, precipitating separation (Mead, 2002). Ultimately, a combination of these factors could contribute to a higher likelihood of relationship instability for higher and lower androgenic men at Cebu.

Complementing these findings linking androgenicity to relationship stability, we found a number of significant interactions between men's T and CAGn in predicting their investments in paternal care. At follow-up, among all men who were fathers, those with shorter CAGn and elevated waking T were more likely to be uninvolved fathers, whereas if their T was low they were relatively likely to be involved in caregiving. We hypothesized that we would observe stronger relationships between androgenicity and current fathering. In light of these cross-sectional analyses, we can only speculate on why we found limited evidence for such an association. Recent results from a small but intensive study of U.S. couples from the pre- to post-partum period found that fathers whose T declined more steeply across their partners' pregnancies reported higher relationship satisfaction and investment, as did their partners. Men's partners also rated them as more supportive after the baby arrived if the fathers showed more of a T decrease. Finally, fathers were more involved in infant care (but only for male infants) if their T declined more steeply (Edelstein et al., 2015, 2016; Saxbe et al., 2016). While our longitudinal study has many strengths, the design is not well suited to test analogous hypotheses because the data collections are separated by ~4.5 years and involve single biomarker collections at each time point. One possibility is that *changes in T* during comparatively shorter measurement windows and during critical life and familial events (such as the transition to parenthood) are more predictive of mother-father-child relational dynamics and thus would show stronger interactive effects with CAGn. In the context of current fathering, androgenicity might likewise be more strongly linked to the quality of men's parenting (e.g. sensitivity, nurturance, synchrony)(Feldman, 2007; Weisman et al., 2014), rather than the sheer quantity, as our measures evaluate. Further longitudinal studies are needed to explore these possibilities.

We also tested whether men's pre-fatherhood androgenicity, at baseline, related to their later caregiving as dads, at follow-up. Thus, these analyses evaluated whether androgenicity before young adult males transitioned to parenthood was predictive of their subsequent fathering, measured 4.5-years later. We found that men who were highly androgenic at age 21–22 years before becoming fathers were less likely to be involved in day-to-day caregiving at follow-up. Demonstrating the robustness of these findings, we found similar results for both of our measures of paternal care and a number of the interactions were significant and in the same direction for both AM and PM T. Additionally, non-fathers who were moderately androgenic (shorter CAGn + lower T; longer CAGn + higher T) were likely to be invested caregivers at follow-up when they became dads.

Meanwhile, low androgenic men also tended to perform minimal childcare. We hypothesized this would be the case in light of research showing that low T is a risk factor for depressive symptoms for some males (reviewed in Ebinger et al., 2009), particularly those with longer CAGn (Harkonen et al., 2003; Sankar and Hampson, 2012; Schneider et al., 2011; Vermeersch et al., 2010; cf. Seidman et al., 2001) and among some fathers (Gettler and Oka, 2016). Consistent with this perspective, fathers' depression in the post-partum period interferes with effective parenting (Ramchandani et al., 2005). However, as we discussed above, men's depressive symptoms in this sample did not vary based on androgenicity. Although we cannot entirely rule out connections with depression and negative mood, this suggests that low androgenicity (before fatherhood) is linked to later paternal care through another pathway. Overall, our results suggest that a moderate level of androgenicity, *before* men become fathers in Cebu, is the androgenic profile that is most predictive of later involved fathering.

One possible explanation for these results is that they reflect a developmental effect of T on neural systems during the prenatal or early postnatal periods (Alexander, 2014; Auyeung et al., 2009; Berenbaum and Beltz, 2011; Hines, 2011; Kuzawa et al., 2010; Wallen, 2005) as well as

adolescence and young adulthood (Bramen et al., 2012; Peper et al., 2011; Raznahan et al., 2010; Schulz et al., 2009). Longitudinal analyses of cortical and sub-cortical maturation from late childhood into young adulthood (age 22) showed that "masculinization" of brain areas that contribute to sexually dimorphic behaviors is more pronounced for subjects with shorter CAGn profiles, implicating an effect of AR genotype on neuronal connectivity (Raznahan et al., 2010). Males with these T-related neural profiles in the prefrontal cortex and limbic areas (e.g. the amygdala) engage in more aggressive behavior from childhood to adulthood (Nguyen et al., 2016), and one of the core neural pathways through which elevated T contributes to competitive and reactive aggressive behavior is via reductions in prefrontal cortical control over amygdala activity (Carré and Olmstead, 2015). Although we lack comparable brain imaging data for our sample, these or similar neural developmental effects of CAGn could help explain why highly androgenic men show tendencies towards later relationship dissolution as well as lower paternal investment at Cebu.

Consistent with existing psychobiological frameworks (Flinn et al., 1998; Gettler, 2016; van Anders et al., 2011; van Anders, 2013; van Anders et al., 2015), an alternative, or complementary, interpretation of these findings is that the social and behavioral experiences that males have from adolescence to young adulthood help to shape their adult T production. Those social neuroendocrine effects then interact with their genotype (CAGn) to predict a trajectory of behavior (later relationship instability, low paternal investment) that is both reflective of being highly androgenic but also likely contributes to the maintenance of elevated T production. For example, van Bokhoven et al. (2006) found that teenagers' T was not strongly linked to their delinquency behaviors (when the two were measured together during adolescence), but a history of delinquency across those teenage years predicted higher T at age 21. Somewhat similarly, Booth and Osgood (1993) found greater juvenile delinquency partially explained later-life relationships between high T in adulthood and elevated adult deviancy.

In a previous analysis, we showed that single non-fathers with higher AM T at age 21.5 years were more likely to be married and married fathers 4–5 years later by age 26 (Gettler et al., 2011). In the present analyses, men's CAGn did not moderate those patterns. We also did not find support for related hypotheses that men with a highly androgenic profile would be more likely to become fathers and have a greater number of children. A number of data- and measurement-related issues could help account for these findings. For example, the men in our sample remain relatively young, in their mid 20s at follow-up, and thus as they age we would expect there to be a wider range of variation across the sample in total number of children, which could be influenced by androgenicity. Similarly, in light of the conservative cultural context in Cebu (see below), it is plausible that men underreported having children outside of marriage or in extra-marital relationships, which would lead to an underestimation of reproductive success among more promiscuous men. In that vein, these outcomes might also reflect cultural processes related to sexual behavior and family dynamics at this site, although we acknowledge the limitations of interpreting null results. Cebu is a relatively conservative, predominately Catholic setting in which female promiscuity is frowned upon and families traditionally play a strong role in arranging or approving marriages (Gipson et al., 2012; Medina, 2001). The vast majority of births also occur in the context of long-term, committed relationships (Gipson et al., 2012; Medina 2001). Women and their families may not prefer men with a higher androgenic profile as marital partners if they behave in a mating-oriented manner (Reynolds, 1966). If highly androgenic men are not inclined towards long-term partnering, it might limit their reproductive opportunities in Cebu. These cultural factors may help explain why our results are dissimilar to Butovskaya and colleagues'(2015) recent findings. We do note that while their results show that men with shorter CAGn had greater reproductive success (via aggressiveness) among foragers and pastoralists in Tanzania (Butovskaya et al., 2015), men's fatherhood status (father vs. non-father) and number of children have not been linked to CAGn in multiple other cultural contexts (Gray et al., 2009; Rajpert-De Meyts et al., 2002; von Eckardstein et al., 2001), including Cebu (here).

Our findings for AR CAGn and other recent, related results contribute to our understanding of the evolutionary history of human variation at this locus, as well as T levels more generally, which are moderately-to-highly heritable (Harris et al., 1998; Hong et al., 2001). Given the variable ecologies in which hominins evolved (Potts, 2012), optimal reproductive strategies likely varied through time and across groups. Successful strategies likely occasionally included males being highly competitive/aggressive and minimally involved in offspring care, which is potentially consistent with our findings for highly androgenic men. In contrast, under other circumstances, males would have been more fit by investing in stable long-term partnerships and diverse forms of paternal investment, as is potentially consistent with our findings for more moderate androgenic profiles (Bribiescas et al., 2012; Gettler, 2014; Geary and Flinn, 2001; Gray and Anderson, 2010; Gurven and Hill, 2009; Hrdy, 2009). Meanwhile, our findings linking especially low androgenicity to relationship instability and reduced paternal care suggests pathways through which the lower extremes of the androgenic range might have been selected against. To the extent that paternal investment has been a viable form of reproductive effort for human males, as has been argued (Bribiescas et al., 2012; Gettler 2010; Gettler, 2014; Geary and Flinn, 2001; Gray and Anderson, 2010; Gray and Crittenden, 2014; Gurven and Hill, 2009), our findings are consistent with the idea that variation in CAGn, and perhaps the polygenic phenotype of "androgenicity" more generally, could have been partly maintained through balancing selection (see Ryan and Crespi, 2012 for review and discussion of alternative interpretations). We suggest that balancing selection acting on polygenic androgenicity would have occurred in parallel with selection favoring males' ability to adjust strategies facultatively based on developmental and current conditions (Bribiescas et al., 2012; Del Giudice et al., 2011; Kuzawa and Bragg, 2012; Gettler, 2016; West-Eberhard, 1979).

In summary, the AR CAG genetic locus we examined here is a plausible candidate contributing to between-individual variation in the psychobiology of partnering and parenting and other neuroendocrine-behavioral outcomes relevant to life history strategies. While we did not find that CAGn moderated the response of T to fatherhood at Cebu, we did show that men with higher or lower androgenicity were more likely to experience relationship instability. Men who were either high or low for androgenicity were also most likely to be uninvolved fathers. We suggest that these results help inform our understanding of variation in male reproductive strategies and the individual physiological and genetic differences that underlie it, particularly when viewed against the backdrop of variable ecologies and selection environments faced by our hominin ancestors.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yhbeh.2016.10.012.

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