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Genetic and environmental contributions to age at menarche: Interactive effects of father absence and *LIN28B*

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ABSTRACT

Substantial research and theory over a number of years have linked father absence to earlier age at menarche (AAM). More recent work has centered on explaining the relative genetic and environmental contributions to this correlation. The purpose of the current study was to evaluate the combined effects of father absence and variation in the *LIN28B* gene on AAM. A sample of 300 women (age 18–25) successfully genotyped for two *LIN28B* single nucleotide polymorphisms (SNPs; rs364663 and rs314273) were used to test gene-environment interaction models. Results for both SNPs were consistent with the hypothesis that father absence would attenuate later AAM associated with *LIN28B*. Genetic index analysis of combined *LIN28B* SNPs showed that girls with at least one copy of the T/T genotype had later AAM if they were father present. Study strengths and the implications of GxE research for life history models are discussed.

1. Introduction

Age at menarche (AAM) marks a significant transition point in pubertal development as girls process through a pre-reproductive state into reproductive maturity. This transition may also come with significant negative health and psychosocial consequences however, especially among girls whose AAM is relatively early. Several studies have shown early AAM is related to greater risk for reproductive cancers (Gong, Wu, Vogtmann, Lin, & Wang, 2013), obesity, and cardiovascular disease (Prentice & Viner, 2013); early maturing girls are also at greater risk for psychosocial problems including internalizing problems, substance use/delinquency, earlier onset of sexual behaviors, and greater subjection to sexual harassment (Ellis et al., 2003; Lichty & Campbell, 2012; Mendle, Turkheimer, & Emery, 2007; Mrug et al., 2013; Skoog & Ozdemir, 2016). Discerning the etiology of AAM variation, and potential strategies for intervention, extends beyond adolescent development and into adulthood and has implications for the physical and psychological well-being of women.

Because early menarche has been linked to an array of biopsychosocial issues, intrapersonal (e.g., race, height, weight) and contextual (e.g., socioeconomic status, family structure) factors that predict AAM have been the focus of considerable research. One contextual factor that has been reliably linked to AAM is biological father absence (i.e., separation or divorce of the birth parents followed by absence of the birth father from the home, Ellis, 2004). Although this extant research has demonstrated a replicable empirical phenomena, the causal mechanism of this association continues to be debated. On one hand are models that presume father absence is an environmental pressure that calibrates reproductive timing. On the other hand are models that suggest the association can be attributed to a third variable confound, such as genetic inheritance. Although these areas of inquiry have provided useful insights into possible causes of AAM variation, hypotheses that position genetic and environmental influences in opposition often overlook important gene-environment transactions. In the current study we conceptualize the interplay between genes and father absence on AAM as a gene-environment interaction (GxE) using a molecular genetic approach. We begin by outlining prior theory and research on the father absence-AAM association, discuss genetically informed research aimed at teasing apart genetic and environmental contributions, and review recent evidence from genome-wide association studies (GWAS) that implicate genetic variation in the *LIN28B* gene as material in regulating developmental timing, and develop hypotheses about the combined and conditional effects of father absence and *LIN28B* that have yet to be studied in the father absence literature.

1.1. Evolutionary perspectives on father absence and AAM

Early theorizing regarding why father absence is associated with AAM (and puberty more generally) stemmed from life history theory (see Ellis, Figueredo, Brumbach, & Schlomer, 2009). The central tenet of life history theory is that organisms make (non-conscious) strategic allocations of time and energy into fundamental components of growth and reproduction. Applied to life course development, for example, organisms make trade-offs between investment in somatic effort, which includes growth, development, and physical maintenance, and

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investment in reproductive effort, such as sexual maturation and finding and/or retaining mates (see Ellis et al., 2009 for an extensive review). From this perspective, developmental experiences serve to entrain developmental trajectories toward life history phenotypes that will ultimately match expected adult reproductive ecologies.

In one of the earliest examples of life history theory applied in human developmental research, Draper and Harpending (1982) theorized that experiencing father absence during development is a critical cue for daughter's expected adult reproductive ecology. Father absence specifically was hypothesized to signify that male participation in child rearing is not critical to reproductive success. In such an ecology, faster life history strategies, characterized by earlier maturation and reproduction, would be evolutionarily favorable. From this perspective, early pubertal timing associated with father absence represents an early facet of an overall developmentally calibrated faster life history strategy. Alternatively, father presence is hypothesized to cue that male parental investment is important for reproduction, which favors slower life history strategies, including later developmental timing.

Building from Draper and Harpending (1982), Belsky, Steinberg, and Draper (1991) further hypothesized that early psychosocial stressors in and around the family also contribute to faster life history strategies (Belsky et al., 1991). This theory expanded on Draper and Harpending (1982) by positing that early experience (the first 5 to 7 years) is a sensitive period for calibrating perceptions of resource predictability, the trustworthiness of others, and the utility of interpersonal relationships. Children's experiences that inform these perceptions – including father absence – result in developmental and behavioral patterns that evolved to optimize reproductive success under these varying conditions. As it has come to be called, psychosocial acceleration theory has been generally well supported by empirical research. For example, a recent meta-analysis of research that examined the relation between father absence and AAM showed a small to moderate and statistically significant correlation across a set of 33 studies (Webster, Graber, Gesselman, Crosier, & Orozco-Schember, 2014). This theoretical foundation and empirical support suggests father absence and associated stressors function as evolutionarily important environmental cues for entraining life history development.

1.2. Father absence and age at menarche may be genetically confounded

Although there is empirical support for the association between father absence and AAM, the causal status of father absence continues to be unclear, which stems, in part, from possible genetic confounding (Barbaro, Boutwell, Barnes, & Shackelford, 2017; Mendle et al., 2006). More specifically, psychosocial acceleration theory assumes father absence and associated stressors exogenously act upon AAM resulting in an evolutionarily coordinated phenotype (Belsky et al., 1991). An alternative explanation is that genetic factors are related to both father absence and AAM, which are passed down from father to daughter. Behavioral genetic models show that AAM is highly heritable – approximately 50% – leading to the conclusion that the association between father absence and AAM may be due to common genetic liability (Rowe, 2002).

Evidence that AAM is heritable does not, however, constitute evidence that the association between father absence and AAM is due to a genetic confound since father absence effects could also operate through (non)shared environmental pathways (see Mendle et al., 2006). Surprisingly, there is relatively little research aimed at directly testing these alternative hypotheses and what research does exist is conflicting. Mendle et al. (2006) found that the association between daughters' stepfather exposure (which indicates biological father absence) and AAM was confounded by a shared genetic or environmental factor, but the data did not permit distinguishing between these two sources of variation. In another study, Tither and Ellis (2008) found that father absence was related to earlier age at menarche after controlling for genetic and family-wide confounds (see also Ellis, Schlomer, Butler, & Tilley, 2012). Using a candidate gene approach, Comings, Muhleman, Johnson, and MacMurray (2002) found the X-linked androgen receptor gene (*AR*) was correlated with parental divorce, father absence, and AAM in girls, lending support for the genetic confounding hypothesis. The association between *AR* and father absence was not replicated, however, in a larger sample of Australian women (Jorm, Christensen, Rodgers, Jacomb, & Easteal, 2004). Taken together, these studies are suggestive that while at least a portion of the association between father absence and AAM may be attributed to genetic loading (i.e., heritability), father absence may additionally influence AAM through environmental means.

Genetically informed studies that examine the relative contributions of genes and environments have moved research on life history theory forward by highlighting that genetic effects must be considered to get an accurate picture of putative environmental influences (Barbaro et al., 2017). This approach assumes, however, that genes and environments have independent main effects on phenotypic development. From a biological point-of-view, the genes plus (or versus) environment approach is problematic because genes cannot operate independently from environments (Meaney, 2010). Instead, gene-environment interactions (GxE) are key determinants for understanding how genes and environments co-act in developmental processes that produce complex phenotypes. GxE research is lacking, however, in the study of father absence and AAM. A notable exception, although not centered on father absence, are primary and replication candidate GxE studies (cGxE) that found the effect of early family relationships on AAM was moderated by variation in the estrogen receptor-α gene (*ESR1*; Hartman, Widaman, & Belsky, 2015; Manuck, Craig, Flory, Halder, & Ferrell, 2011). However, father absence was not directly addressed in either of these studies.

1.3. LIN28B, age at menarche, and father absence

Incorporating molecular genetic information into research on father absence and AAM has the potential to move the field further by directly testing the complex interplay between genes and environments. One of the foremost challenges of cGxE research, however, is deciding *which gene* should be studied. Recent progress has been made on this issue and several papers have offered recommendations for gene-choosing strategies (Dick et al., 2015; Schlomer, Cleveland, Vandenbergh, Fosco, & Feinberg, 2015). Collectively, these researchers argue for a more comprehensive approach than has been previously used in cGxE research, which includes considering results from highly powered GWAS. Markers identified by GWAS are particularly good candidates since they have a high *a priori* probability of producing meaningful associations and interactions (Dick et al., 2015). Relevant to the current study, results from five independent GWAS have identified a robust and replicable association between variants linked to the *LIN28B* gene and AAM. He et al. (2009) identified six single nucleotide polymorphisms (SNPs; rs314277, rs314263, rs369065, rs314280, rs4946651, and rs314262) in or upstream from *LIN28B* that reached genome wide significance in a sample of 17,438 women; in a meta-analysis of eight different GWAS ($N = 17{,}510$), Perry et al. (2009) found an association between rs7759938 (near *LIN28B*) and AAM; Ong et al. (2009) showed one SNP in intron 2 of *LIN28B* (rs314276) reached genome-wide significance ($N = 4{,}714$); Sulem et al. (2009) in a study of 15,297 Icelandic women with replication sets from Iceland, Denmark, and the Netherlands found rs314280 was reliably associated with AAM, replicating He et al. (2009); in another meta-analysis of 32 GWAS ($N = 87{,}802$), Elks et al. (2010) also found rs7759938 was strongly related to AAM. This SNP (rs7759938) has also been linked to AAM in non-European ancestry populations including Korean (Hong et al., 2013), Japanese (Tanikawa et al., 2013), and Filipino (Croteau-Chonka, Lange, Lee, Adair, & Mohlke, 2013) samples (see also Witchel, 2016). Importantly, these SNPs are part of a large linkage-disequilibrium (LD) block associated with *LIN28B* and can be identified by two tag-SNPs, which are also

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