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Review

Genome-wide association studies of age at menarche and age at natural menopause

Chunyan He [a,b,*], Joanne M. Murabito [c,d,*]

[a] Department of Public Health, Indiana University School of Medicine, 980 West Walnut Street, R3-C241, Indianapolis, IN 46202, USA
[b] Melvin and Bren Simon Cancer Center, Indiana University, 535 Barnhill Drive, Indianapolis, IN 46202, USA
[c] The National Heart Lung and Blood Institute's Framingham Heart Study, 73 Mount Wayte, Suite 2, Framingham, MA 01701, USA
[d] Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine, 720 East Concord Street, Boston, MA 02118, USA

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ABSTRACT

Genome-wide association studies (GWAS) have been successful in uncovering genetic determinants of age at menarche and age at natural menopause. To date, more than 30 novel genetic loci have been identified in GWAS for age at menarche and 17 for age at natural menopause. These findings have stimulated a plethora of follow-up studies particularly with respect to the functional characterization of these novel loci and how these results can be translated into risk prediction. However, the genetic loci identified so far account for only a small fraction of the overall heritability. This review provides an overview of the current state of our knowledge of the genetic basis of menarche and menopause timing. It emphasizes recent GWAS results and outlines strategies for discovering the missing heritability and strategies to further our understanding of the underlying molecular mechanisms of the observed genetic associations.

Contents

1. Introduction

Menarche (the first menstruation) and menopause are two fundamental biological events in a woman's life signaling the beginning and the end of reproduction (te Velde and Pearson, 2002). Both are linked to a range of health conditions later in life

* Corresponding authors at: Department of Public Health, Indiana University School of Medicine, 980 West Walnut Street, R3-C241, Indianapolis, IN 46202, USA (C. He); The National Heart Lung and Blood Institute's Framingham Heart Study, 73 Mount Wayte, Suite 2, Framingham, MA 01701, USA (J.M. Murabito). Tel.: +1 317 278 3033; fax: +1 317 278 2966 (C. He), tel.: +1 508 935 3461; fax: +1 508 626 1262 (J.M. Murabito).
E-mail addresses: chunhe@iupui.edu (C. He), murabito@bu.edu (J.M. Murabito).

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that extend beyond reproductive health to osteoporosis (Grainge et al., 2001; Ito et al., 1995), cardiovascular disease (Cooper et al., 1999; Cui et al., 2006; Kannel et al., 1976; Rees, 1995; van der Graaf et al., 1997), breast and endometrial cancer (Kaaks et al., 2002; Kvale, 1992; Peeters et al., 1995; Xu et al., 2004), and mortality (Giles et al., 2010; Hu et al., 1999; Jacobsen et al., 2003, 2007; Lakshman et al., 2009; Mondul et al., 2005; Ossewaarde et al., 2005). The timing of menarche and menopause varies substantially between individuals as well as women across different countries and different ethnic groups (Morabia and Costanza, 1998). In the United States, less than 10% of girls start to menstruate before age 11, and 90% of all girls are menstruating by age 14, with a median age of 12.5 years (Anderson et al., 2003). For African American girls menarche occurs significantly earlier than for girls of European ancestry, while girls of Mexican descent are only slightly younger than girls of European ancestry at the time of menarche (Chumlea et al., 2003; Wu et al., 2002). In women of European ancestry, natural menopause occurs at a median age of 51.4 years (range 40–60 years), while African American and Latina women experience an earlier onset (Bromberger et al., 1997; Henderson et al., 2008), and women of Japanese ancestry undergo a later onset of natural menopause (Gold et al., 2001; Henderson et al., 2008).

Reliable menarche data from studies using similar methods and population selection criteria indicate a recent secular trend toward an earlier onset among girls in the United States and Europe (Harris et al., 2008; Herman-Giddens, 2006; Nichols et al., 2006; Onland-Moret et al., 2005; Parent et al., 2003; Wu et al., 2002). In 1990, the mean age of menarche for girls of European and African American ancestry was 12.6 and 12.1 years, respectively, about 3–5 months earlier than in the late 1960s (Wu et al., 2002). In the United States and Europe, there has been suggestive evidence of a secular trend in menopausal age as well (Nichols et al., 2006; Rodstrom et al., 2003). For women born in the United States between 1915 and 1939, the mean age at natural menopause increased from 49.1 to 50.5 years (Nichols et al., 2006). For Europe it has been shown that this trend toward an increasing menopausal age is independent of socioeconomic status, smoking, oral contraceptive use, and hormone therapy (Rodstrom et al., 2003).

Age at menarche and age at natural menopause are complex traits that are influenced by an intricate set of environmental, lifestyle, and genetic factors (Chie et al., 1997; Gold et al., 2001; Kaprio et al., 1995; Meyer et al., 1991; Morris et al., 2010; Treloar and Martin, 1990). An increased body mass index (BMI) and childhood obesity are associated with a younger age at menarche (Biro et al., 2006; Himes et al., 2004; Lee et al., 2007; Styne, 2004). Smoking is associated with an earlier onset of menopause (Bromberger et al., 1997; Do et al., 1998; Gold et al., 2001; Kato et al., 1998), while a higher BMI is associated with later menopause (Kato et al., 1998; Palmer et al., 2003). While environmental and lifestyle factors including BMI and smoking explain only a small proportion of the observed variations in age at menarche (Chie et al., 1997) and age at natural menopause (van Noord et al., 1997), family and twin studies have demonstrated that genetic factors contribute to at least half of the variations in menarcheal (Chie et al., 1997; Kaprio et al., 1995; Meyer et al., 1991; Sharma, 2002) and menopausal age (de Bruin et al., 2001; Murabito et al., 2005a; Snieder et al., 1998; van Asselt et al., 2004b). Both traits are strongly correlated between mothers and daughters (Torgerson et al., 1997; Treloar and Martin, 1990), and family history is a strong predictor for early menarche (Kaprio et al., 1995) and menopause (Cramer et al., 1995). The heritability estimated from family and twin studies ranges from 53% to 74% for age at menarche (Chie et al., 1997; Kaprio et al., 1995; Meyer et al., 1991; Sharma, 2002), and from 44% to 65% for age at natural menopause (de Bruin et al., 2001; Murabito et al., 2005a; Snieder et al., 1998; van Asselt et al., 2004b).

Despite the strong genetic component, very few genes associated with either age at menarche or age at natural menopause have been identified. Prior to the development of genome-wide association studies (GWAS), genome-wide linkage analysis and the candidate gene association approach were the primary methods to identify susceptibility loci for phenotypic traits. The former method requires family data and can detect rare variants with large genetic effects on diseases or traits but is not suitable for the identification of variants with smaller effects; the latter, based on educated guesses as to which genes or pathways are most likely to be associated with a phenotype, is limited by our incomplete knowledge of the function of the human genome, and thus fails to identify important and novel genes or pathways. The GWAS approach is a different strategy to overcome these difficulties encountered in the discovery of novel susceptibility loci for age at menarche and age at natural menopause. Using GWAS, approximately 30 novel susceptibility loci for age at menarche and 17 for age at natural menopause have been identified to date.

This review summarizes recent advances in the field of genetics of age at menarche and age at natural menopause, and discusses current challenges using GWAS as well as future directions to advance our understanding of the genetic basis of reproductive aging.

2. Pre GWAS era: genetics of menarche and menopause timing

2.1. Genome-wide linkage analysis

The logarithm of odds (LOD) score is usually used as an estimate for evidence of linkage. A LOD score $\geqslant 3$ is generally regarded as significant evidence of linkage, whereas a LOD score between 2 and 3 is considered suggestive evidence.

2.1.1. Age at menarche

Four genome-wide linkage analyses of age at menarche have been reported to date (Table 1). In a sample of European ancestry recruited in the United States consisting of sister pairs and other informative relative pairs, Guo et al. (2006a) reported a strong linkage peak at 22q13 (LOD = 3.70), and two other suggestive linkage signals at 22q11 (LOD = 2.68) and 11q23 (LOD = 1.98). A genetic interaction (epistasis) between genomic regions 22q13 and 3q13 was also detected in this study. A bivariate genome-wide linkage scan using the same population found chromosomal region 22q13 (LOD = 3.33) and an additional region 3p25 (LOD = 2.36) that may harbor genes for both age at menarche and bone mineral density (Pan et al., 2008).

In another much smaller genome scan for age at menarche that used sister pairs of European ancestry and was adjusted for menarcheal weight, Rothenbuhler et al. (2006) implicated regions at 16q21 (LOD = 3.33), 16q12 (LOD = 3.12), and 8p12 (LOD = 2.18). These loci might be involved in weight-independent variability of age at menarche. Recently, Anderson et al. (2008) conducted a large genome scan in three populations of European descent. No significant linkage peaks were identified despite the large number of sister pairs. The study reported a suggestive locus on chromosome 12q (LOD = 2.0).

Although several candidate genes might reside in some of these identified regions, the regions are generally broad (>1 Mb), and the specific genes involved have not been identified. Furthermore, none of these linkage studies have been replicated.

2.1.2. Age at natural menopause

Two genome-wide linkage analyses of age at natural menopause have been published to date (Table 1). The first genome-wide linkage study of age at natural menopause was conducted in Dutch sister pairs using a selective sampling scheme restricting