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Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche

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Age at menarche is a marker of timing of puberty in females. It varies widely between individuals, is a heritable trait and is associated with risks for obesity, type 2 diabetes, cardiovascular disease, breast cancer and all-cause mortality¹. Studies of rare human disorders of puberty and animal models point to a complex hypothalamic-pituitary-hormonal regulation^{2,3}, but the mechanisms that determine pubertal timing and underlie its links to disease risk remain unclear. Here, using genome-wide and custom-genotyping arrays in up to 182,416 women of European descent from 57 studies, we found robust evidence ($P < 5 \times 10^{-8}$) for 123 signals at 106 genomic loci associated with age at menarche. Many loci were associated with other pubertal traits in both sexes, and there was substantial overlap with genes implicated in body mass index and various diseases, including rare disorders of puberty. Menarche signals were enriched in imprinted regions, with three loci (*DLK1-WDR25*, *MKRN3-MAGEL2* and *KCNK9*) demonstrating parent-of-origin-specific associations concordant with known parental expression patterns. Pathway analyses implicated nuclear hormone receptors, particularly retinoic acid and γ -aminobutyric acid-B2 receptor signalling, among novel mechanisms that regulate pubertal timing in humans. Our findings suggest a genetic architecture involving at least hundreds of common variants in the coordinated timing of the pubertal transition.

Genome-wide array data were available from up to 132,989 women of European descent from 57 studies. In a further 49,427 women, data were available on up to approximately 25,000 single nucleotide polymorphisms (SNPs), or their proxy markers, that showed sub-genome-wide

significant associations ($P < 0.0022$) with age at menarche in our previous genome-wide association study (GWAS)⁴ (Supplementary Table 1). Association statistics for 2,441,815 autosomal SNPs that passed quality control measures (including minor allele frequency $> 1\%$) were combined across all studies by meta-analysis.

3,915 SNPs reached the genome-wide significance threshold ($P < 5 \times 10^{-8}$) for association with age at menarche (Fig. 1). Using GCTA⁵, which approximates a conditional analysis adjusted for the effects of neighbouring SNPs (Extended Data Fig. 1 and Supplementary Table 2), we identified 123 independent signals for age at menarche at 106 genomic loci, including 11 loci containing multiple independent signals (Extended Data Tables 1–4; plots of all loci are available at <http://www.reprogen.org>). Of the 42 previously reported independent signals for age at menarche⁴, all but one (gene *SLC14A2*, SNP variation rs2243803, $P = 2.3 \times 10^{-6}$) remained significant genome-wide in the expanded data set.

To estimate their overall contribution to the variation in age at menarche, we analysed an additional sample of 8,689 women. 104/123 signals showed directionally concordant associations or trends with menarche timing (binomial sign test $P_{\text{Sign}} = 2.2 \times 10^{-15}$), of which 35 showed nominal significance ($P_{\text{Sign}} < 0.05$) (Supplementary Table 3). In this independent sample, the top 123 SNPs together explained 2.71% ($P < 1 \times 10^{-20}$) of the variance in age at menarche, compared to 1.31% ($P = 2.3 \times 10^{-14}$) explained by the previously reported 42 SNPs. Consideration of further SNPs with lower levels of significance resulted in modest increases in the estimated variance explained with increasingly larger SNP sets, until we included all autosomal SNPs (15.8%, s.e. 3.6%,

Figure 1 | Manhattan and quantile–quantile plot of the GWAS for age at menarche. Manhattan (main panel) and quantile–quantile (QQ) (embedded) plots illustrating results of the genome-wide association study (GWAS) meta-analysis for age at menarche in up to 182,416 women of European descent. The Manhattan plot presents the association $-\log_{10}(P\text{-values})$ for each genome-wide SNP (y axis) by chromosomal position (x axis). The red line

indicates the threshold for genome-wide statistical significance ($P = 5 \times 10^{-8}$). Blue dots represent SNPs whose nearest gene is the same as that of the genome-wide significant signals. The QQ plot illustrates the deviation of association test statistics (blue dots) from the distribution expected under the null hypothesis (red line).

$P = 2.2 \times 10^{-6}$), indicating a highly polygenic architecture (Extended Data Fig. 2).

To test the relevance of menarche loci to the timing of related pubertal characteristics in both sexes, we examined their further associations with refined pubertal stage assessments in an overlapping subset of 10- to 12-year-old girls ($n = 6,147$). A further independent sample of 3,769 boys had similar assessments at ages 12 to 15 years. 90/106 menarche loci showed consistent directions of association with Tanner stage in boys and girls combined ($P_{\text{Sign}} = 1.1 \times 10^{-13}$), 86/106 in girls only ($P_{\text{Sign}} = 6.2 \times 10^{-11}$) and 72/106 in boys only ($P_{\text{Sign}} = 0.0001$), suggesting that the menarche loci are highly enriched for variants that regulate pubertal timing more generally (Supplementary Table 4).

Six independent signals were located in imprinted gene regions⁶, which is an enrichment when compared to all published genome-wide-significant signals for any trait and/or disease⁷ (6/123, 4.8% vs 75/4332, 1.7%; Fisher's exact test $P = 0.017$). Departure from Mendelian inheritance of pubertal timing has not been previously suspected, therefore we sought evidence for parent-of-origin-specific allelic associations in the deCODE Study, which included 35,377 women with parental origins of alleles determined by a combination of genealogy and long-range phasing⁶.

Two independent signals (no. 85a and 85b; rs10144321 and rs7141210) lie on chromosome 14q32 harbouring the reciprocally imprinted genes *DLK1* and *MEG3*, which exhibit paternal-specific or maternal-specific expression, respectively, and may underlie the growth retardation and precocious puberty phenotype of maternal uniparental disomy-14⁸. In deCODE, for both signals the paternally inherited alleles were associated with age at menarche (rs10144321, $P_{\text{pat}} = 3.1 \times 10^{-5}$; rs7141210, $P_{\text{pat}} = 2.1 \times 10^{-4}$), but the maternally inherited alleles were not ($P_{\text{mat}} = 0.47$ and 0.12 , respectively), and there was significant heterogeneity between paternal and maternal effect estimates (rs10144321, $P_{\text{het}} = 0.02$; rs7141210, $P_{\text{het}} = 2.2 \times 10^{-4}$) (Fig. 2; Supplementary Table 5). Notably, rs7141210 is reportedly a *cis*-acting methylation-quantitative trait locus

(QTL) in adipose tissue⁹ (Extended Data Table 5) and the menarche age-raising allele was also associated with lower transcript levels of *DLK1* (Supplementary Tables 6 and 7)¹⁰, which encodes a transmembrane protein involved in adipogenesis and neurogenesis. In deCODE data, the maternally inherited rs7141210 allele was correlated with blood transcript levels of the maternally expressed genes *MEG3* ($P_{\text{mat}} < 5.6 \times 10^{-53}$), *MEG8* ($P_{\text{mat}} = 4.9 \times 10^{-41}$) and *MEG9* ($P_{\text{mat}} = 5.4 \times 10^{-5}$); however, lack of any correlation with the paternally inherited alleles ($P_{\text{pat}} = 0.18$, $P_{\text{pat}} = 0.87$ and $P_{\text{pat}} = 0.37$, respectively) suggests that these genes do not explain this paternal-specific menarche signal.

Signal no. 86 (rs12148769) lies in the imprinted critical region for Prader-Willi syndrome, which is caused by paternal-specific deletions of chromosome 15q11-13 and includes clinical features of hypogonadotropic hypogonadism and hypothalamic obesity¹¹; conversely, a small proportion of cases have precocious puberty. For rs12148769, only the paternally inherited allele was associated with age at menarche ($P_{\text{pat}} = 2.4 \times 10^{-6}$), but the maternally inherited allele was not ($P_{\text{mat}} = 0.43$; $P_{\text{het}} = 5.6 \times 10^{-3}$) (Fig. 2). Recently, truncating mutations of *MAGEL2* affecting the paternal alleles were reported in Prader-Willi syndrome; all four reported cases had hypogonadism or delayed puberty¹¹, whereas paternally inherited deleterious mutations in *MKRN3* were found in patients with central precocious puberty³. It is as yet unclear which of these paternally expressed genes explains this menarche signal.

Signal no. 57 (rs1469039) is intronic in *KCNK9*, which shows maternal-specific expression in mouse and human brain¹². Concordantly, only the maternally inherited allele was associated with age at menarche ($P_{\text{mat}} = 5.6 \times 10^{-6}$), but the paternally inherited allele was not ($P_{\text{pat}} = 0.76$; $P_{\text{het}} = 3.7 \times 10^{-3}$) (Fig. 2). The menarche age-increasing allele was associated with lower transcript levels of *KCNK9* in deCODE's blood expression data when maternally inherited ($P_{\text{mat}} = 0.003$), but not when paternally inherited ($P_{\text{pat}} = 0.31$). *KCNK9* encodes TASK-3, which belongs to a family of two-pore domain potassium channels that regulate neuronal resting membrane potential and firing frequency.

The two remaining signals located within imprinted regions (rs2137289 and rs947552) did not demonstrate either paternal- or maternal-specific association. We then systematically tested all 117 remaining independent menarche signals for parent-of-origin-specific associations with menarche timing and found only four (3.4%) with at least nominal associations ($P_{\text{het}} < 0.05$; Supplementary Table 5), which was proportionately fewer than signals at imprinted regions (4/6 (67.0%), Wilcoxon rank sum test $P = 0.009$).

Three menarche signals were in genes encoding JmjC-domain-containing lysine-specific demethylases (enrichment $P = 0.006$ for all genes in this family); signal no. 1 (rs2274465) is intronic in *KDM4A*, signal no. 37 (rs17171818) is intronic in *KDM3B*, and signal no. 59b (rs913588) is a missense variant in *KDM4C*. Notably, *KDM3B*, *KDM4A* and *KDM4C* all encode activating demethylases for lysine 9 on histone H3, which was recently identified as the chromatin methylation target that mediates the remarkable long-range regulatory effects of *IPW*, a paternally expressed long noncoding RNA in the imprinted Prader-Willi syndrome region on chromosome 15q11-13, on maternally expressed genes at the imprinted *DLK1-MEG3* locus on chromosome 14q32¹³. Examination of sub-genome-wide signals showed another potential locus intronic in *KDM4B* (rs11085110, $P = 2.3 \times 10^{-6}$). Pubertal onset in female mice is reportedly triggered by DNA methylation of the Polycomb group silencing complex of genes (including *CBX7* near signal no. 105), leading to enrichment of activating lysine modifications on histone H3¹⁴. Specific histone demethylases could potentially regulate cross-links between imprinted regions to influence pubertal timing.

Menarche signals also tended to be enriched in or near genes that underlie rare Mendelian disorders of puberty (enrichment $P = 0.05$)^{2,3}. As well as rs12148769 near *MKRN3*, signals were found near *LEPR-LEPROT* (signal no. 2; rs10789181), which encodes the leptin receptor, and immediately upstream of *TACR3* (signal no. 32; rs3733631), which encodes the receptor for neurokinin B. A further variant approximately 10 kilobases (kb) from *GNRH1* approached genome-wide significance (rs1506869,

Figure 2 | Forest plot of parent-of-origin-specific allelic associations at three imprinted menarche loci. The forest plot illustrates the associations of variants in four independent genomic signals for age at menarche that are located in three imprinted gene regions. For each variant, squares (and error bars) indicate the estimated per-allele effect sizes on age at menarche in years (and 95% confidence intervals) from the standard additive models in the combined ReproGen meta-analysis (grey), and separately for the paternally inherited (blue) or maternally inherited allele (red) in up to 35,377 women from the deCODE study. The association for the menarche locus with the largest effect size at *LIN28B* is also shown for reference, illustrating the similar magnitude of effect size at the *MKRN3* locus when parent-of-origin is taken into account.

$P = 1.8 \times 10^{-6}$) and was also associated with *GNRH1* expression in adipose tissue ($P = 3.7 \times 10^{-5}$). Signals no. 34 (rs17086188) and 103 (rs852069) lie near *PCSK1* and *PCSK2*, respectively, indicating a common function of the type 1 and 2 prohormone convertases in pubertal regulation. Signals in or near several further genes with relevance to pituitary development/function included: signal no. 20 (rs7642134) near *POU1F1*, signal no. 39 (rs9647570) within *TENM2*, and signal no. 42 (rs2479724) near *FRS3*. Furthermore, signals no. 71 (rs7103411) and no. 92 (rs1129700) are *cis*-expression QTLs (eQTLs) for *LGR4* and *TBX6*, respectively, both of which encode enhancers for the pituitary development factor *SOX2*. Signals no. 52 (rs6964833) intronic in *GTF2I* and no. 104 (rs2836950) intronic in *BRWD1* were found in critical regions for complex conditions that include abnormal reproductive phenotypes, Williams–Beuren syndrome (early puberty)¹⁵ and Down syndrome (hypogonadism in boys), respectively¹⁶.

Including signals described above, we identified 29 menarche signals in or near genes with possible roles in hormonal functions (Fig. 3, Supplementary Table 8), many more than the three signals we described previously (*INHBA*, *PCSK2* and *RXRG*)⁴. Two signals were found in or near genes related to steroidogenesis. Signal 35 (rs251130) was a *cis*-eQTL for *STARD4*, which encodes a StAR-related lipid transfer protein involved in the regulation of intra-cellular cholesterol trafficking. Signal no. 9 (rs6427782) is near *NR5A2*, which encodes a nuclear receptor with key roles in steroidogenesis and oestrogen-dependent cell proliferation.

We observed that SNPs in or near a custom list of genes that encode nuclear hormone receptors, co-activators or co-repressors were enriched for associations with menarche timing (enrichment $P = 6 \times 10^{-5}$). Individually, nine genome-wide significant signals mapped to within 500 kb of these genes, including those encoding the nuclear receptors for oestrogen, progesterone, thyroid hormone and 1,25-dihydroxyvitamin D3. Several nuclear hormone receptors are involved in retinoic acid signalling. SNPs in or near *RXRG* and *RORA* reached genome-wide significance, and three other genes contained sub-genome-wide signals (*RXRA* (rs2520094, $P = 4 \times 10^{-7}$), *RORB* (rs4237264, $P = 9.4 \times 10^{-6}$), *RXRB* (rs241438, $P = 7.1 \times 10^{-5}$)). Two other genome-wide significant signals mapped to genes with roles in retinoic acid function (no. 67 *CTBP2* and no. 101 *RDH8*). The active metabolites of vitamin A, all-*trans*-retinoic acid and 9-*cis*-retinoic acid, have differential effects on gonadotropin-releasing hormone (GnRH) expression and secretion¹⁷. Other possible mechanisms linking retinoic acid signalling to pubertal timing include inhibition of embryonic GnRH neuron migration, and enhancement of steroidogenesis and gonadotropin secretion¹⁸. The relevance of our findings to observations of low circulating vitamin A levels and use of dietary vitamin A in delayed puberty¹⁹ are yet unclear.

To identify other mechanisms that regulate pubertal timing, we tested all SNPs genome-wide for collective enrichment across any biological pathway defined in publicly available databases. The top ranked pathway reaching study-wide significance (false discovery rate = 0.009) was gamma-aminobutyric acid (GABA_B) receptor II signalling (Extended Data Table 6); each of the nine genes in this pathway contained a SNP with sub-genome-wide significant association with menarche (Extended Data Table 7). Notably, GABA_B receptor activation inhibits hypothalamic GnRH secretion in animal models²⁰.

Regarding the relevance of our findings to other traits, we confirmed⁴ and extended the overlap between genome-wide significant loci for menarche and adult body mass index (BMI)²¹. At all nine loci (in or near *FTO*, *SEC16B*, *TMEM18*, *NEGR1*, *TNNI3K*, *GNPDA2*, *BDNF*, *BCDIN3D* and *GPRC5B*) the menarche age-raising allele was also associated with lower adult BMI (Supplementary Table 9). Three menarche signals overlapped known loci for adult height²². The menarche age-raising alleles at signals no. 47c (rs7759938, *LIN28B*) and no. 83 (rs1254337, *SIX6*) were also associated with taller adult height, which is directionally concordant with epidemiological observations. Conversely, the menarche age-raising allele at signal no. 48 (rs4895808, *CENPW-NCOA7*) was associated with shorter adult height (Supplementary Table 9).

Further menarche signals overlapped reported GWAS loci for other traits, but in each case at only a single locus, therefore possibly reflecting small-scale pleiotropy rather than a broader shared genetic aetiology. Signal no. 26 (rs900400) was a *cis*-eQTL for *LEKR1*, and is the same lead SNP associated with birth weight²³. The menarche age-raising allele was also associated with higher birth weight, directionally concordant with epidemiological observations²⁴. Signal no. 48 (rs4895808, a *cis*-eQTL for *CENPW*) is in linkage disequilibrium (LD) ($r^2 = 0.90$) with the lead SNP for the autoimmune disorder type 1 diabetes, rs9388489²⁵, which also showed robust association with menarche timing ($P = 6.49 \times 10^{-12}$). Signal no. 41 (rs16896742) is near *HLA-A*, which encodes the class I, A major histocompatibility complex, and is a known locus for various immunity or inflammation-related traits⁷. Signal no. 50 (rs6933660) is near *ESR1*, which encodes the oestrogen receptor, a known locus for breast cancer²⁶ and bone mineral density²⁷. Notably, the menarche age-raising allele at rs6933660 was associated with higher femoral neck bone mineral density ($P = 6 \times 10^{-5}$)²⁷, which is directionally discordant with the epidemiological association²⁸. Signal no. 70 (rs11022756) is intronic in *ARNTL*, a known locus for circulating plasminogen activator inhibitor type 1 (PAI-1) levels²⁹; the reported lead SNP (rs6486122) for PAI-1²⁹ also showed robust association with menarche timing ($P = 9.3 \times 10^{-10}$).

Our findings indicate both BMI-related and BMI-independent mechanisms that could underlie the epidemiological associations between

Figure 3 | Schematic diagram indicating possible roles in the hypothalamic-pituitary-ovarian axis of several of the implicated genes and biological mechanisms for menarche timing.

early menarche and higher risks of adult disease¹. These include actions of *LIN28B* on insulin sensitivity through the mTOR pathway, GABA_B receptor signalling on inhibition of oxidative stress-related β -cell apoptosis, and *SIRT3* (mitochondrial sirtuin 3), which could link early life nutrition to metabolism and ageing. Finally, only few parent-of-origin-specific allelic associations at imprinted loci have been described for complex traits⁶. Our findings implicate differential pubertal timing, a trait with putative selection advantages³⁰, as a potential additional target for the evolution of genomic imprinting.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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- Prentice, P. & Viner, R. M. Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. *Int. J. Obes.* **37**, 1036–1043 (2013).
- Silveira, L. F. G. & Latronico, A. C. Approach to the patient with hypogonadotropic hypogonadism. *J. Clin. Endocrinol. Metab.* **98**, 1781–1788 (2013).
- Abreu, A. P. et al. Central precocious puberty caused by mutations in the imprinted gene *MKRN3*. *N. Engl. J. Med.* **368**, 2467–2475 (2013).
- Elks, C. E. et al. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nature Genet.* **42**, 1077–1085 (2010).
- Yang, J. et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nature Genet.* **44**, 369–375 (2012).
- Kong, A. et al. Parental origin of sequence variants associated with complex diseases. *Nature* **462**, 868–874 (2009).
- Hindorf, L. A. et al. A catalog of published genome-wide association studies. Available at <http://www.genome.gov/gwastudies>. (Accessed, 1 November 2013).
- Temple, I. K., Shrubbs, V., Lever, M., Bullman, H. & Mackay, D. J. G. Isolated imprinting mutation of the *DLK1/GTL2* locus associated with a clinical presentation of maternal uniparental disomy of chromosome 14. *J. Med. Genet.* **44**, 637–640 (2007).
- Grundberg, E. et al. Global analysis of DNA methylation variation in adipose tissue from twins reveals links to disease-associated variants in distal regulatory elements. *Am. J. Hum. Genet.* **93**, 876–890 (2013), corrected **93**, 1158 (2013).
- Westra, H.-J. et al. Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nature Genet.* **45**, 1238–1243 (2013).
- Schaefer, C. P. et al. Truncating mutations of *MAGEL2* cause Prader-Willi phenotypes and autism. *Nature Genet.* **45**, 1405–1408 (2013).
- Ruf, N. et al. Sequence-based bioinformatic prediction and QUASEP identify genomic imprinting of the *KCNK9* potassium channel gene in mouse and human. *Hum. Mol. Genet.* **16**, 2591–2599 (2007).
- Stelzer, Y., Sagi, I., Yanuka, O., Eiges, R. & Benvenisty, N. The noncoding RNA *IPW* regulates the imprinted *DLK1-DIO3* locus in an induced pluripotent stem cell model of Prader-Willi syndrome. *Nature Genet.* **46**, 551–557 (2014).
- Lomniczi, A. et al. Epigenetic control of female puberty. *Nature Neurosci.* **16**, 281–289 (2013).
- Partsch, C.-J. et al. Central precocious puberty in girls with Williams syndrome. *J. Pediatr.* **141**, 441–444 (2002).
- Grinspon, R. P. et al. Early onset of primary hypogonadism revealed by serum anti-Müllerian hormone determination during infancy and childhood in trisomy 21. *Int. J. Androl.* **34**, e487–e498 (2011).
- Cho, S. et al. 9-cis-Retinoic acid represses transcription of the gonadotropin-releasing hormone (GnRH) gene via proximal promoter region that is distinct from all-trans-retinoic acid response element. *Brain Res. Mol. Brain Res.* **87**, 214–222 (2001).
- Nagl, F. et al. Retinoic acid-induced nNOS expression depends on a novel PI3K/Akt/DAX1 pathway in human TGW-nu-1 neuroblastoma cells. *Am. J. Physiol. Cell Physiol.* **297**, C1146–C1156 (2009).
- Zadik, Z., Sinai, T., Zung, A. & Reifen, R. Vitamin A and iron supplementation is as efficient as hormonal therapy in constitutionally delayed children. *Clin. Endocrinol.* **60**, 682–687 (2004).
- Constantin, S. et al. GnRH neuron firing and response to GABA *in vitro* depend on acute brain slice thickness and orientation. *Endocrinology* **153**, 3758–3769 (2012).
- Speliotes, E. K. et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nature Genet.* **42**, 937–948 (2010).
- Lango Allen, H. et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* **467**, 832–838 (2010).
- Horikoshi, M. et al. New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism. *Nature Genet.* **45**, 76–82 (2013).
- D'Aloisio, A. A., DeRoo, L. A., Baird, D. D., Weinberg, C. R. & Sandler, D. P. Prenatal and infant exposures and age at menarche. *Epidemiology* **24**, 277–284 (2013).
- Barrett, J. C. et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nature Genet.* **41**, 703–707 (2009).
- Zheng, W. et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. *Nature Genet.* **41**, 324–328 (2009).
- Estrada, K. et al. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. *Nature Genet.* **44**, 491–501 (2012).
- Parker, S. E. et al. Menarche, menopause, years of menstruation, and the incidence of osteoporosis: the influence of prenatal exposure to diethylstilbestrol. *J. Clin. Endocrinol. Metab.* **99**, 594–601 (2014).
- Huang, J. et al. Genome-wide association study for circulating levels of PAI-1 provides novel insights into its regulation. *Blood* **120**, 4873–4881 (2012).
- Migliano, A. B., Vinicius, L. & Lahr, M. M. Life history trade-offs explain the evolution of human pygmies. *Proc. Natl Acad. Sci. USA* **104**, 20216–20219 (2007).

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Author Information Plots of all 106 menarche loci and genome-wide summary level statistics are available at the ReproGen Consortium website: <http://www.reprogen.org>. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to J.R.B.P. (john.perry@mrc-epid.cam.ac.uk) and J.M. (murabito@bu.edu).

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