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

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 mortality (1). 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 gamma-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.