Hundreds of Genomic Regions Linked to Age at Menarche

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NEW YORK (GenomeWeb) – An international team of researchers has uncovered nearly 400 genomic regions associated with age at menarche.

Age at onset of puberty is affected by a combination of genetic, nutritional, and other environmental factors and that timing, in turn, is associated with risk of cancer later in life.

By turning to genome-wide array data from some 330,000 women imputed to the 1000 Genomes Project reference panel, a University of Cambridge- and DeCode Genetics-led team of researchers identified hundreds of signals linked to age at menarche, as they reported in *Nature Genetics* today. They traced some of these signals to genes expressed in neural tissue and noted variants near paternally imprinted genes. The researchers also reported an inverse association between puberty onset and breast, endometrial, and prostate cancers.

"[O]ur findings suggest unprecedented genetic complexity in the regulation of puberty timing and support new causal links with susceptibility to sex steroid-sensitive cancers in women and men," the researchers led by DeCode's Kari Stefansson and Cambridge's Ken Ong and John Perry wrote in their paper.

The researchers folded together data from 40 studies from the ReproGen Consortium with data from 23andMe and UK Biobank studies to yield data from 329,345 women of European ancestry. They imputed this genome-wide array data to the 1000 Genomes Project reference panel, and uncovered 389 variants associated with age at menarche.

They replicated these signals in 39,543 additional women from a DeCode study, and noted that 368 retained genome-wide significance in a combined meta-analysis.

Overall, the researchers estimated that the top index SNPs explain slightly more than 7 percent of variance in age at menarche. They also noted that there was a strong link between these signals and ones linked to voice breaking in men.

With a combination of nonsynonymous SNP mapping, expression quantitative trait locus mapping, and examination of Hi-C chromatin interaction data, the researchers homed in on a number of genes linked

to age at menarche. For instance, they noted nonsynonymous variants within genes previously linked to puberty disorders such as aromatase, gonadotropin-releasing hormone, and kisspeptin. With Hi-C data, they further uncovered potential distal causal genes like INHBA, BDNF, and RORB.

A pathway analysis likewise implicated peptide hormone binding, PI3-kinase binding, angiotensin-stimulated signaling, neuron development and g-aminobutyric acid-type B receptor signaling pathway in puberty timing.

At the same time, they found that five GTEx tissues were enriched for age at menarche-related variants. As the researchers noted, all of these tissues were from the central nervous system, and included the pituitary.

The researchers also reported that a number of the variants associated with age at menarche were located near imprinted genes with parent-of-origin effects. In particular, they found variants in both MKRN3 and DLK1 that are associated with age at menarche under a paternal, but not maternal, model.

Since a complex relationship has previously been noted between puberty timing, BMI, and cancer risk, the researchers investigated genetic correlations between them to find an inverse genetic correlation between age at menarche and BMI.

In a Mendelian randomization analysis — adjusted for predicted BMI — the researchers further reported that increasing age at menarche was associated with a lower risk of breast cancer, especially estrogen receptor-positive breast cancer, and of ovarian cancer.

They also noted a protective effect of later puberty on prostate cancer in men.

"The influences of earlier puberty timing, independent of BMI, on higher risks of breast, ovarian and endometrial cancers in women and prostate cancer in men could be mediated by a longer duration of exposure to sex steroids," the researchers wrote.

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