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12 DNA areas 'linked with the age at which we have our first child and family size'

Researchers have identified 12 specific areas of the DNA sequence that are robustly related with the age at which we have our first child, and the total number of children we have during the course of our life. The study, led by the University of Oxford, working together with the Universities of Groningen, The Netherlands and Uppsala, Sweden, includes an analysis of 62 datasets with information from 238,064 men and women for age at first birth, and almost 330,000 men and women for the number of children. Until now, reproductive behaviour was thought to be mainly linked to personal choices or social circumstances and environmental factors. However, this new research shows that genetic variants can be isolated and that there is also a biological basis for reproductive behaviour. The paper is co-authored by over 250 sociologists, biologists, and geneticists from institutions worldwide, and has been published in the journal *Nature Genetics*.

Lead author Professor Melinda Mills, from the Department of Sociology and Nuffield College at the University of Oxford, comments: 'For the first time we now know where to find the DNA areas linked to reproductive behaviour. For example, we found that women with DNA variants for postponing parenthood also have bits of DNA code associated with later onset of menstruation and later menopause. One day it may be possible to use this information so doctors can answer the important question: "How late can you wait?" based on the DNA variants. It is important to put this into perspective, however, as having a child still strongly depends on many social and environmental factors that will always play a bigger role in whether or when we have babies.'

The study shows that DNA variants linked with the age at which people have their firstborn are also associated with other characteristics reflecting reproduction and sexual development, such as the age at which girls have their first period, when the voice breaks in boys, and at what stage women experience their menopause.

First author Nicola Barban, from the Department of Sociology and Nuffield College at the University of Oxford, comments: 'Our genes do not determine our behaviour, but for the first time, we have identified parts of the DNA code that influence it. This is another small piece to understanding this very large jigsaw puzzle.'

The researchers calculated that variants in the 12 areas of the DNA together predict less than 1% of the timing at which men and women have their first child and of the number of children they have in the course of their lifetime. The paper says that while these numbers seem 'extremely small', their modelling shows that in some cases when the variants are combined, they can be used to predict the probability of women remaining childless. Importantly, by examining the function of the 12 DNA regions and the genes in these regions in detail, the researchers have identified 24 genes that are likely to be responsible for the effects of the 12 DNA variants on reproductive behaviour. Some of these genes were already known to influence infertility, while others have not yet been studied. According to study co-authors Professor Harold Snieder from the University of Groningen and Associate Professor Marcel den Hoed from Uppsala University, 'an improved understanding of the function of these genes may provide new insights for infertility treatments'.

For more information, please contact the University of Oxford News Office on news.office@admin.ox.ac.uk; Tel: +44 (0)1865 280534.

Notes for Editors

*The paper, 'Genome-wide analysis identifies 12 loci influencing human reproductive behavior' is published in the scientific journal, *Nature Genetics*. It is strictly embargoed until Monday, 31 October 2016 at 1600 London time / 1200 US Eastern time. Once live, it will appear at http://dx.doi.org/10.1038/ng.3698

*Films about the research findings of this paper and the Sociogenome project, including an interview with lead author Professor Melinda Mills, are available for use by media. For more details, please contact news.office@admin.ox.ac.uk

*Sociogenome is a research project located at the University of Oxford and Nuffield College, funded by the European Research Council and led by Professor Melinda Mills. The project is a comprehensive study of the role of genes and gene-environment (GxE) interaction on reproductive behaviour. Until now, social science research has focussed on socio-environmental explanations, largely neglecting the role of genes. Drawing from recent unprecedented advances in molecular genetics, it examines whether there is a genetic component to reproductive outcomes, including age at first birth, number of children and infertility and their interaction with the social environment. See http://www.sociogenome.com/

*Researchers from 175 institutions and departments were involved in the study. Funding for the project was provided through grants to Mills from an ERC Consolidator Grant SOCIOGENOME (615603), a Dutch Science Foundation (NWO) grant (VIDI grant 452-10-012), UK ESRC/NCRM SOCGEN grant (ES/N011856/1), European Union's FP7 FamiliesAndSocieties project (no.320116) and the Wellcome Trust ISSF & John Fell Fund. Den Hoed was supported by grants from the Swedish Research Council (2015-03657) and the Swedish Heart-Lung Foundation (20140543).

*Professor Melinda Mills's main research areas are currently in the area of combining a social science and genetic approach to the study of behavioural outcomes, with a focus on fertility, partnerships and assortative mating. She is currently the Editor-in-Chief of the European Sociological Review and a Fellow of the European Academy of Sociology. See: http://www.melindacmills.com

Researchers give fuller explanation of the findings

What is 'human reproductive behaviour'? How was it measured?
Human reproductive behaviour is defined by two measures: age at first birth (AFB) and number of children ever born (NEB). AFB is the self-reported age when subjects had their first child. In most cases, people were directly asked a question such as: "How old were you when you had your first child?" Alternatively, researchers calculated the measure based on several survey questions (e.g., date of birth of the individual and the date of birth of their first child). Number of children ever born (NEB) is the self-reported number of children that an individual has. It was often asked directly such as "How many children do you have?" They also calculated it based on several survey questions (for example, pregnancy histories and outcomes, number of deliveries). NEB has emerged as the gold standard to measure lifetime reproductive success indicating 'biological fitness'.

Why the findings are timely given trends in modern society?
In many industrialized societies, first-time parents are considerably older than decades before, which in turn has consequences for the number of children they can have and their reproductive health. Since the 1970s, there has been a rapid postponement by around 4-6 years in the age at first birth from women having their first child at around 24 years in 1970 to 29 years in 2012 in many industrialized societies. There has not only been postponement, but also significant increases in the levels of childlessness, with around 20-25% of women born from 1965-69 in Southern and Western European countries having no children. The

biological ability to conceive a child starts to steeply decline for some women as of age 25, with almost 50% of women being sterile by the age of 40.5 This means that a growing number of women start to have their first and subsequent children exactly at the time that their ability to conceive starts to decrease. Birth postponement and a lower number of children has been largely attributed to social, economic and cultural environmental factors (i.e., individual and partner characteristics, socioeconomic status), with virtually no attention paid to the genetic or biological underpinnings of this behaviour.

How the researchers studied the genome
They searched across the entire human genome, examining each genetic locus (or region) one by one to see if there is a relationship (or what we call an association) between our outcomes (AFB, NEB) and a particular genetic locus. These genetic loci contain so-called SNPs (pronounced SNIPs), which refers to single-nucleotide polymorphisms, or in other words, the DNA variants that distinguish us from each other. In the largest GWAS on human reproduction to date, they combined results from 62 different studies into what is referred to as a meta-analysis with a total sample size of N=251,151 for AFB and N=343,072 for NEB. They also performed separate meta-analyses for women (AFB, N=189,656; NEB, N=225,230) and men (AFB, N=48,408; NEB, N=103,909). They went beyond simply finding the location of the genetic loci to determine whether they had any biological function or relevance. They identified 12 independent loci (10 of which were not previously anticipated to influence reproductive behaviour) that were significantly associated with AFB and/or NEB.

The main finding
They found that **all** 12 genetic loci **combined** can explain around 1 % of the variability in the average age at which someone has their first baby. They can also predict around 0.2% of the variability of the number of children we will have in the course of our lifetime using a combined polygenic score. Although it may seem low, the results showed that a 1 standard deviation increase of the NEB polygenic score is associated with a 9% decrease in the probability for women to remain childless (with no significant effect found for men).

Could these results help predict exact timing of first child and number of children people will have?
No – not at all. As described previously, since each individual SNP or genetic variant has such a small effect, prediction of AFB or NEB using genetic results alone is not possible. Even if they combine the genetic variants together into an index or what is termed a ‘polygenic score’ using all approximately 9 million SNPs in our data, they can still only predict 0.9% and 0.2% of the variation in AFB and NEB across individuals. As more and more genetic data becomes available, they anticipate that it will be possible to predict at most 15 to 20% of the variance in AFB and NEB, which would resemble more recent whole-genome results.

Do the genetic variants identified have relevance for fertility treatments?
A variable that predicts around 1% of the variation in human reproductive behaviour is large enough to be relevant and useful for experts in many disciplines. In the longer term, this study offers a better understanding of the genetic architecture of human reproductive behaviour. It likewise has the potential to enable the discovery of predictors of infertility, which would in turn greatly improve family planning but also increase the effectiveness of costly and invasive ART treatments as well as allow couples to realize their fertility intentions. Some of the lead SNPs or genetic loci are related to critical fertility related processes such as: follicle stimulating hormone, estrogen, growth in ovaries, spermatid differentiation, male germ cell development and diseases associated with female infertility

(endometriosis, PCOS).
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