Early Childhood DNA methylation & Its Developmental Consequences

http://www.newscientist.com/article/dn20255-childhood-poverty-leaves-its-mark-on-adult-genetics.html

Childhood poverty leaves its mark on adult genetics

- 16:30 26 October 2011 by **Andy Coghlan**

Genes can be reset during early life in profoundly different ways depending on whether children grow up in privileged or deprived households, a landmark study has shown.

Although children in rich and poor households have very similar sets of genes, the scale of adversity at home dictates which combinations of those genes are switched on or silenced through a process called epigenesis – presumably to maximise the chance of survival.

"They may be protective responses, and the payoff is surviving a threatening childhood," says Marcus Pembrey from the University of Bristol, UK, who co-authored the study whilst working at University College London's Institute of Child Health.

The penalty might be activation of genes that make poorer people more prone to heart disease, diabetes, cancer and other diseases. That could help explain why poorer people often have shorter lives. Epigenetic changes have also recently been linked to conditions that can involve psychosis, including schizophrenia and bipolar disorder.

Haves and have-nots

Pembrey and his colleagues selected 40 men from a group of 3000 born in 1958 – half born into rich households and half born into poor ones. "We selected subjects from the top and bottom 20 per cent according to socioeconomic status, so ensuring we had examples of both extremes," says Pembrey.

The team took blood samples from the men when they were 45, and screened their DNA for any epigenetic changes. They were looking for chemical markings that either silence or activate individual genes. Genes that are methylated – those that have had extra methyl groups added at some stage – tend to be switched off, whereas demethylated groups – having lost methyl groups – are activated.

Focusing on stretches of DNA called promoter regions, which turn genes on or off, the team examined more than 20,000 sites throughout the genome. They found patterns that varied with the wealth or poverty of the men's childhood homes.

The patterns were different between the two groups at almost a third of the sites. Most tellingly, methylation levels were drastically different at 1252

sites if men came from poor households, but only at 545 sites in men from rich backgrounds.
"It's telling us that the epigenetic changes in adult DNA are largely from early life experience," says Pembrey.

Uncertain age

Because the samples were taken in middle age, the researchers couldn't tell exactly when the epigenetic methyl groups were added or subtracted. "We can't say whether the genes were altered in infancy, childhood, fetal life or even the previous generation," says Pembrey. But whenever they were added, they survived to middle age.

Next, Pembrey and his colleagues hope to find out when these changes happen by studying the stored blood of children who took part in the Avon Longitudinal Study of Parents and Children. This project has tracked since birth 14,000 people born in the Bristol area; most are now aged around 20. The blood samples, including cord blood, have been taken every few years. "We can see whether epigenetic patterns are constant from cord blood onwards, or pick up signals from the environment and get reset right up to puberty," says Pembrey.

Many of the affected genes, such as a group called MAP kinases, have functions relating to the signals accepted by cells. What's more, the epigenetic changes tended to be in defined clusters rather than random individual changes, suggesting that entire networks of genes were simultaneously silenced or activated epigenetically.

"They're like huge coordinated switches, as if the whole genome is flipping," says Pembrey. He speculates that the gene networks activated or silenced by these processes are then permanently embedded in the genome. This could cause alterations that blind people to external signals or make them more sensitive to them, he says. Such changes could make people unusually sensitive to threatening situations – useful if they encounter such situations regularly during childhood.

Down the generations

"The paper strengthens the idea that environmental conditions early in life can persistently modify the epigenome and may influence health," says Isabelle Mansuy of the University of Zurich in Switzerland. "But prenatal conditions may also play a role and cannot be excluded," she says.
Last year, Mansuy led a landmark study showing that epigenetic changes in mice deliberately stressed during childhood could be passed down to at least two generations of descendants.

Reference: *International Journal of Epidemiology*, DOI: 10.1093/ije/dyr147

Associations with early-life socio-economic position in adult DNA methylation

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Accepted August 25, 2011.

Abstract

Background Disadvantaged socio-economic position (SEP) in childhood is associated with increased adult mortality and morbidity. We aimed to establish whether childhood SEP was associated with differential methylation of adult DNA.

Methods Forty adult males from the 1958 British Birth Cohort Study were selected from SEP extremes in both early childhood and mid-adulthood. We performed genome-wide methylation analysis on blood DNA taken at 45 years using MeDIP (methylated DNA immunoprecipitation). We mapped in triplicate the methylation state of promoters of approximately 20 000 genes and 400 microRNAs. Probe methylation scores were averaged across triplicates and differential methylation between groups of individuals was determined. Differentially methylated promoter sites of selected genes were validated using pyrosequencing of bisulfite-converted DNA.

Results Variably methylated probes (9112 from $n = 223\ 359$ on the microarray) corresponded to 6176 gene promoters with at least one variable probe. Unsupervised hierarchical clustering of probes obtained from the 500 most variable promoters revealed a cluster enriched with high SEP individuals confirming that SEP differences contribute to overall epigenetic variation.

Methylation levels for 1252 gene promoters were associated with childhood SEP vs 545 promoters for adulthood SEP. Functionally, associations with childhood SEP appear in promoters of genes enriched in key cell signalling pathways. The differentially methylated promoters associated with SEP cluster in megabase-sized regions of the genome.
Conclusions Adult blood DNA methylation profiles show more associations with childhood SEP than adult SEP. Organization of these associations across the genome suggests a well-defined epigenetic pattern linked to early socio-economic environment.
Key words

- 1958 British birth cohort
- adult DNA methylation profile
- childhood socio-economic position
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