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NEWS AND COMMENTARY

Epigenetics

Sins of the fathers, and their fathers

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A fascinating article by Marcus Pembrey and co-workers,[1] published in this issue of the European Journal of Human Genetics, suggests that the behaviour (or environment) of prepubescent boys could influence the phenotype of their sons and grandsons.

Using data collected in the Avon Longitudinal Study of Parents and Children (ALSPAC), they showed that early paternal smoking was associated with greater body mass index at 9 years of age in sons, but not in daughters. This prompted them to return to the records of the 1890, 1905 and 1920 cohorts from Overkalix, an isolated community in Northern Sweden. Previously, they reported an association of ancestral food supply with longevity[2] and with cardiovascular and diabetic mortality.[3]

Reanalysis showed that the paternal grandfathers' food supply during mid childhood was linked to the mortality risk ratio of grandsons, but not granddaughters. The study suggested that in humans, a one-off environmental event could influence phenotype for more than one generation in a sex-specific way. If true, these findings implied a novel kind of transgenerational inheritance, an idea strengthened by recent studies in animal systems.

The effects of maternal nutrition or other environmental 'exposures' are well recognised in mammals, including humans. Epidemiological studies from the UK have demonstrated an association between low birth weight and adult onset disease, including heart disease and diabetes.[4] While the relative importance of genetic and environmental factors in this phenomenon remains unclear, most interpret it as an example of the effects of maternal undernutrition.

In animal models, these types of effects, termed fetal programming, can be produced by exposing offspring *in utero* to a manipulation such as dietary restriction of the pregnant female.[5] Although most studies of fetal programming only address effects in the first-generation offspring, there is strong evidence that, at least in some cases, these programmed phenotypes are maintained for several generations.[6] For example, prenatal programming of birth weight by maternal food restriction or maternal exercise have been shown to last for more than one generation.[7,8]

The molecular basis for these apparently nongenetic transgeneration effects is not known. One hypothesis is that it involves epigenetics. Epigenetics is the process by which patterns of gene expression are modified in a mitotically heritable manner by mechanisms that do not involve DNA mutation. Epigenetic modifications include, among others, the methylation state of the DNA and the proteins that package the DNA into chromosomes. The epigenetic state of the genome is established in early development and is generally thought to be cleared between generations.

However, there is increasing evidence that some parts of the genome are not cleared leading to transgenerational inheritance of epigenetic state in these specific parts, termed transgenerational epigenetic inheritance.[9–11] Furthermore, the establishment of the epigenetic state at these loci can be modified by environment. For example, the epigenetic state of the *agouti viable yellow* locus, containing a gene contributing to coat colour in mice, can be manipulated by altering the diet of the pregnant female.[12,13] At this stage, these effects have only been studied in F1 offspring. However, epigenetics does provide a possible mechanism for the transgenerational effects reported by Pembrey and co-workers.

Their intriguing finding of transgenerational effects that are sex-specific, is also not without precedent in animal systems. It has been known for some time that transient exposure of pregnant female rats to vinclozolin, a fungicide used in the wine industry, can cause reproductive abnormalities in male offspring.[14] A recent study[15] has shown that the reproductive abnormalities, including reduced sperm count and sperm motility, are detected in nearly all male offspring for at least four generations. The effect could not be passed through female subjects; female siblings of affected males in the F2 generation, when mated with untreated controls, produced male offspring with normal fertility.

The authors favour the idea that the toxin causes epigenetic changes to the DNA in the developing germ line of the male embryos, and that this change is maintained and carried along with the sperm to the next generation. However a role for the Y chromosome, similar to that postulated by Pembrey, remains a possibility.

There are many intriguing parallels between the rat study from the Skinner lab and the Pembrey study in humans. Geneticists, epigeneticists and environmental biologists are still grappling with these surprising results. Whether this is a new kind of genetic event, which is Y-specific, or an epigenetic event that is sperm-specific, or something else altogether, remains unclear. However, the implications of the finding are profound.

From a public health point of view, what makes the Pembrey study particularly interesting is that it argues that exposure in the male can affect the development and health of males for at least two generations, and this is rarely, if ever, considered. This paper should stimulate both epidemiologists

and experimental biologists to look for transgenerational effects in other situations. Furthermore, these findings may go some way toward shifting the balance of responsibility for the unborn, away from the mother. Fathers-to-be take note!

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