Epigenetic interactions

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Environmental cues influence the epigenetic state of our genomes, and thereby modulate our cellular responses to the environment. In mammals this machinery seems to act, at least in part, through reproducible and reversable changes to the methylation state of specific CpG nucleotides, although there is some debate as to whether DNA methylation is a marker for rather than the actual agent of change. It is also the case that in mammals the identity of the parent of origin of a chromosome silences, or otherwise dysregulates, the expression of about 100 imprinted genes (in humans fewer; more in mice).[1] Near these genes, the methylation of specific nucleotides tracks the chromosomes' parent of origin and is therefore implicated in the mechanism of imprinted gene silencing. In addition, some CpGs unlinked to imprinted genes exhibit parent-of-origin specific methylation.[2]

Logically, the next question is whether the environment and parent of origin interact. That is, are any methylated CpG nucleotides under the control of both phenomena? Where so, we expect to see a complex pattern of DNA methylation that cannot be explained by either factor alone. A difficulty of testing this hypothesis in humans is the lack of large samples of people whose genotypes are phased with respect to parent of origin and with DNA methylation data, preferably from a relevant tissue. At present, only a few ingeniously repurposed datasets are available.

In this issue Zeng *et al* [3] address these questions in 2,315 individuals from Generation Scotland: The Scottish Family Health Study.[4] In this cohort a sizable fraction of individuals has phased genotypes inferred from parental genotypes, together with extensive phenotypes and some methylation data from blood. A previous study of the same cohort [2] had identified 2,372 methylation quantitative trait loci (mQTL) at CpG islands that were also associated with parent of origin effects; Zeng *at al* then mined these sites for environmental interactions. This two stage analysis strategy was necessary to maintain statistical power, given the relatively small sample size. The sample was further divided into discovery (1,663) and replication (652) sets, corresponding to different sub-cohorts. Although replication reduces the power to detect associations, it increases the likelihood that reported findings are correct.

The authors report four methylated nucleotides with replicated environmental interactions (with lifetime smoking or predicted mRNA expression), implicating three genes, namely *SIRT1, TET2* and *KDM1A*. None of these genes are thought to be imprinted, so the consequences of parent-of-origin effects on their nearby methylated nucleotides remain to be clarified. However, each of these genes could plausibly mediate genome-wide epigenetic interactions. The most noteworthy candidate is *SIRT1*. This de-acetylase has a wide range of protein interactions (e.g. with *DNMT1*), has genome-wide effects on DNA methylation,[5] and is implicated in many diseases, ranging from diabetes to depression. Similarly *TET2* mutations are associated with DNA hypermethylation.[6] Lastly, the histone demethylase *KDM1A* binds to *DNMT1* and helps maintain genome-wide DNA methylation.[7]

The relatively small sample size means only a few replicated interactions are reported. This is unsurprising given that the Scottish Family Health Study was not designed for this analysis. However, the findings suggest it would be worthwhile to investigate a much larger cohort with phased genotypes (likely to become feasible as more families are sequenced), with environmental histories such as smoking and diet, and where methylation data is available. The latter requirement is probably the most difficult to achieve, especially if inaccessible tissues are required; therefore it is likely the focus will continue to be on methylation in blood (ie white cells) in the near future. In theory, methylation in other tissues could be imputed,[8] given deep training data, although one would need to take into account environmental exposure and parent of origin for this context.

This is also a situation where carefully designed experiments with rodent models could provide insights. Reciprocal crosses of inbred strains of mice [9] enable the animals' environment to be rigorously controlled (for example high fat vs low fat diet), their genotypes phased with respect to parent of origin, and imprinted gene expression and DNA methylation measured in appropriate tissues. Such designed experiments are much smaller than observational studies in humans, reflecting the ability to control the environment and to assay relevant tissues. On the other hand, more genes are imprinted in mice than in humans and not all human environmental exposures are understood well enough to establish an appropriate animal model. Thus, animal studies are likely to be best at dissecting the fundamental biology of epigenetic interactions.

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From a clinical perspective, we need to ask how to structure observational studies in human cohorts to benefit patients the most. That is, given methylation data from a patient's blood (or possibly another tissue if a biopsy is performed), together with phased genotypes and a full patient history, how much better could diagnosis, treatment and outcome become from what is possible now from (say) a combined environmental and polygenetic risk score, or from general advice to lose weight or not smoke? There is certainly room for improvement because so much remains to be understood.

Declaration of interests

The author Richard Mott declares no conflict of interests.

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