these disorders directly and indirectly lead to further non-endocrine morbidity. Thus, while monitoring for and managing endocrine disorders in existing cancer survivors, we must continue to investigate new curative cancer treatments that have less potential to cause endocrine and other serious late effects. Several national groups and the International Late Effects of Childhood Cancer Guideline Harmonization Group[10] continue to evaluate the evidence systematically and develop clinical guidelines for screening of asymptomatic childhood cancer survivors.

Kevin C Oeffinger, Charles A Sklar
Departments of Medicine (KCO) and Pediatrics (KCO, CAS), Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
oeffingk@mskcc.org

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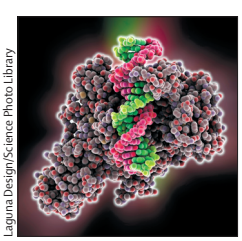
Epigenetics in health and disease: heralding the EWAS era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DNA methyltransferase

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Success in the identification of genetic variants that affect complex human phenotypes, such as height, weight, and common diseases, is one of the major achievements in contemporary biomedical research. Insight into the functional complexity of the genome also draws attention to the probable role of non-sequence-based genomic variation in health and disease. Notably, substantial attention is focused on the role of epigenetic processes that might regulate gene expression via modifications to DNA, histone proteins, and chromatin in medical traits. Although the role of epigenetic mechanisms in some rare developmental syndromes and in cancer is well established, systematic examination of their contribution to common non-malignant disease phenotypes is only just beginning.

New microarray-based and sequencing-based technologies allow economical, high-throughput profiling of epigenetic marks, with a primary focus on DNA methylation; the era of the epigenome-wide association study (EWAS) of large numbers of samples has begun. In *The Lancet*, Katherine Dick and colleagues describe the first systematic analysis of the association between variation in DNA methylation and body-mass index (BMI).[1] They report significant associations between methylation at three probes targeting specific CpG sites within intron 1 of *HIF3A* and BMI in a discovery cohort, and subsequently confirm them in two independent cohorts. For every 10% increase in methylation of the most significant probe—cg22891070—BMI increased by 3·6% (95% CI 2·4–4·9), equating to about 0·98 kg/m² for a person in the discovery cohort with a BMI of 27 kg/m² on average.[1] The increase in BMI was higher in individuals who had had a myocardial infarction (4·6%, 2·9–6·3) than in blood donors (2·3%, 0·4–4·1).[1] To put the size of this epigenetic association into perspective, the minor allele of *FTO*—robustly associated with obesity-related traits—accounts for a more modest 0·39 kg/m² increase in BMI.[2] *HIF3A* encodes a component of the hypoxia inducible transcription factor that mediates the cellular response to hypoxia by regulating expression of many downstream genes.[3] This transcription factor has been previously implicated in metabolism[4] and obesity,[5] providing a biologically plausible mechanism behind the reported association with BMI.

Epigenetic epidemiology is an area of great research interest; in the past year, EWAS have been reported for several other human health phenotypes, such as multiple sclerosis,[6] rheumatoid arthritis,[7] pain sensitivity,[8] and metabolic traits.[9] Dick and colleagues[1] used a powerful

sequential-replication design to do one of the most systematic epigenetic studies of a human physiological phenotype yet reported. However, the results of any EWAS need to be interpreted carefully, with clear caveats when compared with genetic studies of complex traits. Unlike genetics, a range of potentially important confounding factors need to be considered, such as tissue or cell type, age, sex, drug exposure, and reverse causation.[10]

A primary concern in epigenetic epidemiology is the tissue-specific nature of the epigenome. In large well-phenotyped sample cohorts, such as the discovery cohort used in Dick and colleagues' study,[1] DNA from peripheral tissues (normally whole blood) is often the only source of biological material available. To circumvent this issue, Dick and colleagues subsequently examined the relation between DNA methylation at their top-ranked loci and BMI in adipose and skin tissue from an independent sample cohort, recording strong associations in adipose tissue but not skin.[1] Furthermore, the investigators examined the correlation between DNA methylation and *HIF3A* expression in adipose tissue, reporting a significant inverse correlation and drawing attention to the potential functional relevance of epigenetic variation at the identified locus. This result is important, because it suggests that assessment of DNA methylation in whole blood can identify robust and biologically relevant epigenetic variation related to BMI.

Of course, blood itself is a heterogeneous mix of epigenetically distinct cell types, with variation in cell counts between individuals a potentially huge confounder in EWAS analyses. Dick and colleagues included basic cell-count data that allowed some control for cellular heterogeneity;[1] another approach is the use of robust algorithms to infer cellular composition from epigenomic data.[11] However, if the cellular content of a tissue is strongly associated with the trait being studied—as is likely for inflammatory or neurodegenerative disorders, for example—any apparent trait-associated epigenetic differences could partially reflect differences in cellular composition, even after statistical correction.

Another important issue concerns the ability to distinguish between cause and effect. For example, the epigenetic variation reported by Dick and colleagues[1] could have arisen before any alteration in BMI, contributing directly to obesity-related phenotypes. Alternatively, it could represent a secondary, downstream effect of variation in BMI itself or another exposure associated with variation in BMI. Therefore, the most robust design for epigenetic epidemiology involves the longitudinal assessment of epigenetic changes within the context of a prospective cohort study, so that epigenetic variation can be related to temporal changes in exposures and phenotype.[10]

Dick and colleagues attempt to address the issue of causality by applying a mendelian randomisation approach[12] to interrogate the causal relation between *HIF3A* methylation and BMI. This approach uses a genetic proxy for DNA methylation (namely, methylation quantitative trait loci) to identify a causal relation between an exposure or trait and epigenetic variation, assuming that genetic associations are largely immune to residual confounding and reverse causation. Dick and colleagues identified two upstream single nucleotide polymorphisms that were independently associated with DNA methylation at a *HIF3A* locus in both the discovery and replication cohorts. However, these single nucleotide polymorphisms were not associated with BMI in the study cohorts or the high-powered GIANT consortium dataset,[13] suggesting that hypermethylation at the *HIF3A* locus is likely to be a result of increased BMI rather than a causal association between increased methylation and BMI. A non-causal association between methylation and a phenotype could still be informative as a diagnostic or prognostic biomarker—eg, *HIF3A* methylation might predict disease phenotypes associated with BMI, such as cancer and cardiovascular disease.

Dick and colleagues' study[1] represents an important advance for both obesity-related research and the specialty of epigenetic epidemiology. BMI is a good phenotype for population-based epigenomic studies: it is an accurate measure that is routinely collected in most cohort studies. The widespread uptake of instruments such as the Illumina 450K HumanMethylation array means that large collaborative EWAS meta-analyses can be done, building on the success of similar approaches in genetics.[13] Whether EWAS will be as successful for other clinical phenotypes—especially those manifest in more inaccessible tissues such as brain, or more directly affected by confounding factors such as cellular heterogeneity, environmental exposures, and drugs—remains to be seen.

*Therese M Murphy, *Jonathan Mill*
Medical School, University of Exeter, Royal Devon and Exeter Hospital, Exeter EX2 5DW, UK (TMM, JM); and Institute of Psychiatry, King's College London, London, UK (JM)
j.mill@exeter.ac.uk

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UK funders' framework for health-related findings in research

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Researchers who undertake studies that involve human participants sometimes face a dilemma: what steps, if any, should they take if their research data reveal something about the current or future health of an individual? Making a judgment on the appropriate way to respond to a finding is complicated, particularly in situations in which participants might have no symptoms related to the finding; there is no medical history; there are no clinicians in the research team; and a decision has to be made on findings that do not meet standards of clinical quality or a validated diagnostic test. Although there might be a compelling argument to provide, or not to provide, feedback to participants in some cases, often the situation is far from clear.

The lack of clarity in the research community about how to respond to health-related findings does not seem to accord with public attitudes. Respondents in a UK survey of 1105 members of the public showed strong support for informing research participants about health-related findings, particularly when findings relate to a condition that is serious and treatable.[1] To maintain public trust in health research it is crucial that researchers consider the issues that arise from health-related findings so that they are able to justify their approach and explain it to potential research participants. Given the current absence of accessible guidance for researchers, the Wellcome Trust and Medical Research Council (MRC) have worked in collaboration with the Health Research Authority to develop a framework to support researchers as they consider these matters.[2]

There is a diverse range of health-related findings and situations in which they might arise during research. Researchers might discover pertinent findings that relate to the aims of the study, but could also detect incidental findings, which have been defined as "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study".[3] Health-related findings can be identified through different investigations, such as imaging, genetic tests, and physiological measurements and assays, including blood tests. Furthermore, research with human participants encompasses different types of studies, including clinical trials, non-interventional studies, and longitudinal or stand-alone studies.

Despite much debate, there is little consensus on whether, and if so how, health-related findings should be returned to participants. Within the UK, practices around health-related findings vary widely between disciplines and institutions.[4] Guidance is, however, beginning to emerge in some areas: for example, The Royal College of Radiologists has produced recommendations for the management of incidental findings in research imaging.[5] A range of approaches is also emerging internationally: the Canadian Tri-Council Policy Statement[6] requires researchers "to disclose to the participant any material