Editorial: Current Opinion in Behavioral Sciences Special Issue on Genetic Imprinting and Behaviour

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An organism's behaviour represents the complex culmination of its genetics, the environments it experiences throughout its life, and stochastic developmental processes. One of the key goals in biology has been to understand, at the molecular level, how exposure to particular experiences can interact with genetics to give rise to individualised behaviour patterns. For example, we know that, although monozygotic twins share exactly the same DNA, they can be quite divergent in how they think and act (Haque et al., 2009).

Over the past 30 years, work in the field of epigenetics has started to systematically address this question. Epigenetics is the study of chemical marks which affect the structure and expression of the genome, without altering its sequence. In the strictest sense, the term 'epigenetic' should only be used to describe those marks which are heritable across cellular divisions; now however, it is used more fluidly (and controversially) to cover a range of processes, including those which might technically be more accurately referred to as 'transcriptional regulation' (Deans and Maggert, 2015). Epigenetic marks range from those which modify the DNA at discrete sites (notably methylation or hydroxymethylation at CpG dinucleotides), to modification of the histone proteins involved in local chromatin structure (often via acetylation or methylation), to non-coding RNAs which can coat extensive genomic regions. Importantly, epigenetic marks are labile and can be affected by the cellular milieu; hence, they represent a fascinating molecular nexus between an organism's genetics and its environment.

Epigenetic studies may provide insights into how the unique genetic and environmental factors experienced by an individual can influence behavioural and cognitive processes, for example with respect to personality and memory function (Sweatt). However, often behavioural epigenetic studies are correlational (identifying differences in epigenetic signatures between phenotypically-distinct groups which may not necessarily be causal), and rely on epigenetic information obtained from peripheral tissues rather than brain. The use of model systems, in which environmental exposures can be controlled and where brain tissue can be readily accessed, can circumvent these issues. Here, McCarthy reviews recent work in rodents in which epigenetic effects (notably in the preoptic area of the hypothalamus) are shown to mediate the development of sexually-dimorphic behaviours, whilst Anreiter et al. review advances in understanding the relationship between epigenetic signatures and behaviour in the invertebrate fruitfly *Drosophila melanogaster*. Whether the associations and processes observed in these systems are also seen in humans remains to be tested.

We know from genetic studies that genes encoding mediators of epigenetic processes seem to be disproportionately highly-mutated in developmental and psychiatric disorders (Mastrototaro et al., 2017; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015); hence, as well as being useful for understanding normal variation in behavioural function, epigenetic studies may also be relevant for understanding the biology of pathological conditions. Work in this area is particularly challenging, as distinct epigenetic signatures between healthy individuals and individuals with a psychiatric diagnosis may be causal, or may simply reflect differential environmental exposures across groups (e.g. increased rates of smoking, stress, general poor health or drug consumption in cases compared to controls). On a more positive note, access to large samples of brain tissue from patient cohorts is becoming increasingly feasible, allowing more biologically (and therapeutically) meaningful links between neural epigenetic signatures and disorder status to be discovered. Here, Bastle and Maze describes new findings regarding how chromatin regulation may influence the risk of multiple brain disorders, whilst Migdalska-Richards and Mill focus on exciting new work identifying epigenetic signatures associated with schizophrenia in peripheral and brain tissues. Two review papers then touch on the fascinating overlap between circadian biology and depression and the epigenetic signatures underlying these (Shi and Johnson and Sato and Sassone-Corsi), with a view to characterising potential novel therapeutic strategies.

One of the most interesting, and controversial, areas of research in behavioural epigenetics over the past few years has been the inter-generational transmission of behavioural phenotypes. For example, good and bad rodent mothers may differentially affect the epigenetic status of genes involved in the stress response in their offspring (and subsequent offspring behaviour) via high or low levels of maternal care respectively (Weaver et al., 2004). Alternatively, situations experienced by parents may be encoded epigenetically in the germline, and may, ultimately, lead to altered behaviour in offspring (Dias and Ressler, 2014). Jawaid and Mansuy critically review some of these animal model studies, as well as examining the concept that inheritance of epigenetic correlates of parental experiences may occur in humans.

DNA in the paternal and maternal germlines is differentially epigenetically-marked, hence the need for a parent of either sex to produce viable offspring. In the offspring, whilst most genes are equally expressed from their paternal and maternal copies, epigenetic processes ensure that a handful of genes are only expressed from the paternally-inherited copy, and a small number of genes only from their maternally-inherited copy. These so-called 'imprinted genes' are known to regulate important developmental processes, and there is an increasing recognition of their important role in neurodevelopment and behaviour (Wilkinson et al., 2007). Prader-Willi syndrome (PWS) is a neuroendocrine condition caused by loss-of-function of paternally expressed genes on chromosome 15q11-13, and is characterised by an impaired satiety response; Whittington and Holland review the complex range of neurobehavioural issues in individuals affected by PWS and examine genotype-phenotype correlations. Interestingly, individuals with PWS as a consequence of a maternal duplication of 15q11-13 are more likely to exhibit psychotic phenotypes than individuals with other genetic mutations. Crespi critically reviews the evidence that paternally and maternally expressed imprinted genes more generally may be oppositely associated with developmental and psychiatric disorder risk. The behavioural phenotype of patients with PWS is likely to be influenced, in

part, by imprinted small non-coding RNAs; these molecular regulators are likely to influence a range of other normal and aberrant brain functions, and their established roles have been comprehensively reviewed by Marty and Cavaille.

Whilst the functions of imprinted genes such as those within the PWS interval, are relatively well-understood, there is not yet a concensus as to how many (and which) genes are imprinted, and exactly what processes they regulate. Ho-Shing and Dulac describe emerging work, primarily in elegant mouse models, which has screened for, and identified, novel imprinted genes and which has begun to dissect their biological functions. More focussed, single gene led work covered by Isles et al. has highlighted imprinted genes as potential mediators of offspring behavioural phenotypes following early-life adversity, whilst work assessed here by Lassi and Tucci has implicated imprinted genes in sleep processes. The evolutionary pressures which have led to the establishment and maintenance of genomic imprinting in mammals remain to be clarified. Theoretically, genomic imprinting could be influenced by, and influence, dispersal processes (Hitchcock and Gardner).

The reviews in this Special Issue serve to highlight the fact that we are currently at the very early stages of understanding how epigenetic mechanisms, including genomic imprinting, are associated with, and might be causal for, behavioural phenotypes and disorder risk. Over the next decade, we expect to see a substantial improvement in the efficacy and accuracy with which we can interrogate the complete epigenome, as well as in the availability of highly-selective epigenome-modifying drugs and manipulations permitting tests of causality.

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