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Current Opinion in Behavioral Sciences

Behavioural effects of imprinted genes

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The importance of imprinted gene effects on brain and behaviour is becoming increasingly clear. In addition to roles in neurodevelopmental disorders such as Prader–Willi and Angelman syndromes, changes in expression of imprinted genes contribute to neuropsychiatric illness more generally. Imprinted genes are also critical for placental function, and can influence adult behavioural outcomes via effects on the supply and demand of nutrients from the mother. Finally, the high level of epigenetic regulation and parental specific monoallelic expression make this subset of mammalian genes candidates for mediating the behavioural effects of exposure to an adverse pre-natal and/or post-natal environment. Here we provide an overview of recent developments in our understanding of the different mechanisms via which imprinted genes can influence behaviour.

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Current Opinion in Behavioral Sciences 2015, **2**:28–33

This review comes from a themed issue on **Behavioral genetics**

Edited by **William Davies** and **Laramie Duncan**

For a complete overview see the Issue and the Editorial

Available online 4th August 2014

http://dx.doi.org/10.1016/j.cobeha.2014.07.008

Introduction

Imprinted genes represent a unique sub-set of genes that, despite having both maternal and paternal alleles present in the genome, are expressed from one parental allele only. Imprinted genes are often found in clusters, although some exist in microdomains encompassing just a single imprinted protein coding gene [1]. It is thought that all imprinted gene expression is initiated and ultimately dependent on parental specific DNA methylation of DMRs (differentially methylated regions) laid down in the germline [2]. Following fertilisation, the initial epigenetic marks are subsequently built upon with other modifications in order to robustly maintain the imprinting status in the somatic tissues. This occurs through a combination of non-coding RNA, additional DNA methylation, changes in histone modifications and higher chromatin structure [2]. The result of these parental specific epigenetic marks is that some imprinted genes are only expressed from the maternally derived allele (maternally expressed), whilst others are only expressed from the paternally derived allele (paternally expressed).

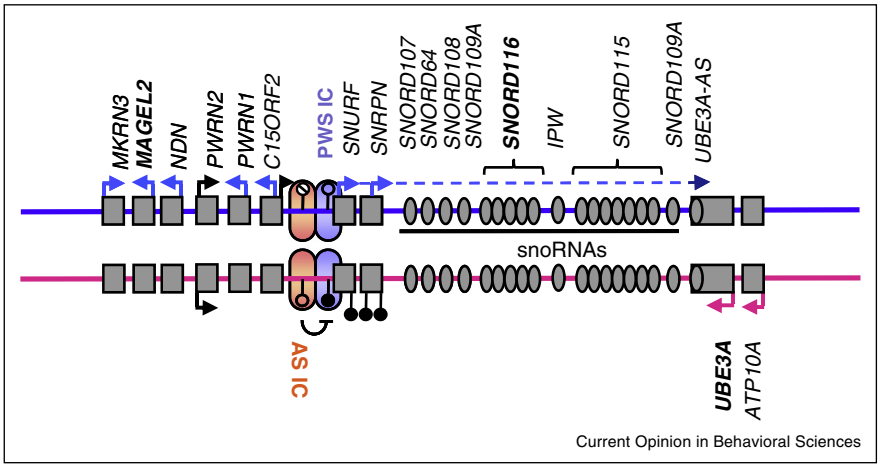
Although research on imprinting has mainly focused on understanding the underlying epigenetic mechanisms [3], imprinted genes also influence some key physiologies specifically *in utero* growth and placental function [4], energy homeostasis [5] and brain development and behaviour [6]. The focus of this review is on the latter, although we will also touch upon the role of the placenta. Specifically, the aim here is to examine recent studies of where imprinted genes have been shown to influence behaviour.

Angelman/Prader–Willi syndrome interval

Loss of maternal or paternal gene expression from the 15q11-q13 imprinted interval leads to Angelman (AS) and Prader–Willi (PWS) syndromes respectively [6]. Given their association with these neurodevelopmental disorders, the imprinted genes in this interval have been the most studied in terms of their contribution to brain and behaviour. For instance, human genetic and animal model studies have demonstrated that loss of expression of the maternally expressed gene *UBE3A* is the key cause of AS [6]. Indeed, a novel therapeutic technique is centred on reactivation of the normally silent paternal copy of *UBE3A* using topoisomerase inhibitors which, in a mouse model of AS, rescues the gene expression loss [7]. In addition to loss of expression being important for brain function, over-expression of *UBE3A* is also thought to be a major contributing factor to the neuropsychiatric problems associated with maternal micro-duplications spanning the 15q11-q13 interval [8].

Similar efforts have been made to identify a 'PWS gene'. However, here the story is less clear-cut, with many more paternally expressed genes in the interval, loss of which probably contributes to the overall PWS phenotype (Figure 1). Nevertheless, recent attention has focused on two of these genes as being key. A number of clinical cases with unique but overlapping microdeletions at 15q11.2, leading to loss of the paternal copy of the *SNORD116* small nucleolar (sno)RNAs, also displayed

Figure 1



Schematic showing a representative imprinted gene cluster, in this case, the AS/PWS imprinted cluster on human chromosome 15. As is common for imprinted genes, within this cluster are both paternally (blue arrows) and maternally (pink arrows) expressed genes. Also marked with black 'lollipops' is the DMR, which in the case of the AS/PWS locus is methylated on the maternally derived chromosome. The key genes of interest in relation to AS (*UBE3A*) and PWS (*SNORD115* and *MAGEL2*) are indicated in bold.

the same failure to thrive, hypotonia, and hyperphagia that is observed in PWS patients with larger deletions and maternal uniparental disomy [9•,10–12]. Lending support to the idea that *SNORD116* plays a central role in PWS, *Snord116del* knockout mice bear many characteristics reminiscent of the human PWS phenotype, including postnatal growth retardation and failure to thrive [13,14]. Abnormal adult behaviours include increased anxiety/fear, motor learning deficiency and an apparent failed satiety response [13]. Although thought to be involved in the regulation of alternative splicing via its interaction with long non-coding RNAs [15], the mechanism by which *SNORD116* results in these behavioural changes is not clear. Interestingly, very recent evidence has highlighted the importance of *IPW*, another non-coding RNA in the aetiology of PWS through its regulation of separate imprinted loci, the *DLK1-DIO3* cluster [16]. *IPW* is also deleted in all the *SNORD116* deletion clinical cases [9•,16], and expression of *Ipw* is attenuated in neural precursor cells derived from *Snord116del* mice [17]. This suggests that the phenotype seen in both the clinical cases and animal model cannot be wholly ascribed to the action of *SNORD116*.

The advent of next generation sequencing techniques has also pointed to *MAGEL2* as a key contributor to PWS [18•]. Four patients were identified with point mutations in the *MAGEL2* gene that, when paternally derived, leads to a truncated protein rendering individuals without a functional expressed copy of *MAGEL2*. Although the importance of *MAGEL2* in causing PWS *per se* has been questioned [19], *Magel2*-null mice also show some phenotypes consistent with PWS, including hypoactivity and abnormal circadian rhythmicity [20]. Of particular significance however, is the association of the early poor feeding and failure to thrive phenotype with restricted production of bioactive oxytocin (OT) in the hypothalamus of *Magel2* KO new-borns [21]. Among other functions, OT is an anorexigenic hormone which effects feeding control and this led the researchers to test a possible intervention strategy. A single injection of OT before the first 5 hours after birth completely rescued the early mortality by the recovery of normal suckling in *Magel2* KO new-borns [21]. Early administration of OT is now a potentially promising therapeutic for the early failure to thrive and feeding problems seen in PWS newborns.

Grb10, *Igf2* and the developmental programming of behaviour

A fascinating recent example of an imprinted gene impacting upon brain and behaviour is that of the gene encoding the growth factor receptor-bound protein 10 (*Grb10*). Behavioural studies of mice with a paternally inherited null *Grb10* ($Grb10^{+/p}$) demonstrated a role for this gene in social dominance behaviour [22]. The 'tube test' is measure of social dominance that forces an encounter between two unfamiliar animals. The nature of the test apparatus (animals are released simultaneously at opposite ends of a clear, narrow tube that is not big enough for two mice to pass) leads to a subordinate mouse retreating upon meeting a more dominant conspecific. In this task $Grb10^{+/p}$ mutants were found to be significantly less likely to back down and retreat than their wild-type (WT) opponents.

The initial suggestion for a role of paternal expressed *Grb10* in social dominance was found from patterns of