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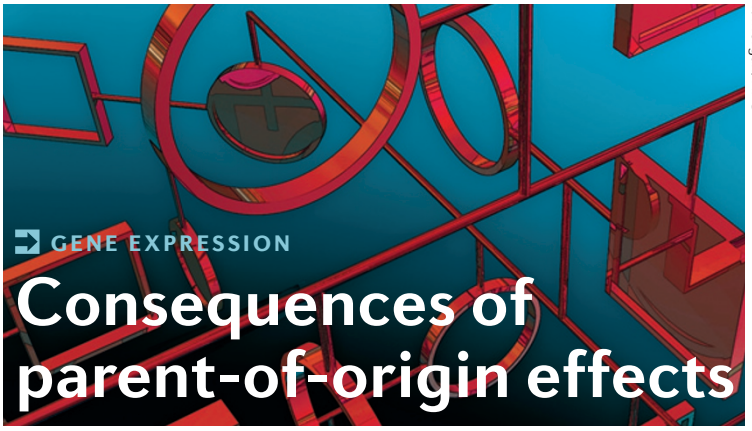

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> classically imprinted genes function together with non-imprinted genes in a wider network

Parent-of-origin effects occur when the phenotypic effects of a gene are determined by whether the gene is inherited from the mother or the father. However, the prevalence and the impact of parent-of-origin effects on the heritability of complex traits are unclear. A new study by Mott and colleagues has shown that, in mice, a surprisingly large number of traits show parent-of-origin effects and that several genes interact with imprinted genes to generate these effects.

Studying parent-of-origin effects in a large population is inherently difficult, as it requires extensive knowledge of the degrees of relatedness within the population. Therefore, Mott and colleagues studied a subset of 97 traits that were previously described from a heterogeneous mice stock, for which the genotypes of both parents were available, in order to determine the parent-of-origin effect on phenotype.

The authors used computational methods to re-analyse published data on these traits and found that 93% of traits were affected by parent of origin. In addition, they identified individual quantitative trait loci (QTLs) with parent-of-origin effects that underlie these traits. Within the identified QTL regions, two candidate genes — *H2-ab1* (histocompatibility 2, class II antigen A, β1) and *Man1a2* (mannosidase-α, class 1A, member 2), which lie at non-imprinted loci — were chosen for further investigation. Using reciprocal mouse crosses in which either the mother or the father carried knockout alleles, the authors confirmed that *H2-ab1* and *Man1a2*, which were not known to be imprinted, caused parent-of-origin effects.

What is the consequence of loss of expression of genes with parent-of-origin effects on the expression of other genes? The authors used RNA sequencing on *H2-ab1* heterozygotes from these reciprocal crosses to address this question and found that loss of *H2-ab1* caused genome-wide gene expression changes in a parent-of-origin-dependent manner. Importantly, these changes were usually twofold increases or decreases, which suggested that monoallelic expression was either induced or abolished. In addition, some known imprinted genes were differentially expressed. This implies that *H2-ab1* generates parent-of-origin effects by dysregulating the expression of imprinted genes that in turn causes changes in a variety of downstream genes.

This study offers insights into the interactions between imprinted and non-imprinted genes. It suggests that classically imprinted genes function together with non-imprinted genes in a wider network and that disruption of this network collectively causes parent-of-origin effects. Furthermore, this work could influence the interpretation of large-scale population studies of complex genetic disease in humans, which do not typically account for parent-of-origin effects, and explain part of the 'missing heritability' in many of these studies.

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ORIGINAL RESEARCH PAPER Mott, R. *et al.* The architecture of parent-of-origin effects in mice. *Cell* **156**, 332–342 (2014)
FURTHER READING Lawson, H.A., Cheverud, J.M. & Wolf, J.B. Genomic imprinting and parent-of-origin effects on complex traits. *Nature Rev. Genet.* **14**, 609–617 (2013)