LINK TO ORIGINAL ARTICLE

Inbreeding effects in the epigenetic era

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Recent articles by Charlesworth and Willis (The genetics of inbreeding depression. *Nature Rev. Genet.* **10**, 783–796 (2009))[1] and Kristensen *et al.*[2] have summarized the theoretical basis of inbreeding depression (the deleterious effects of crossing related individuals). Although overdominance (the fact that heterozygotes are fitter than homozygotes) cannot be entirely ruled out, the expression of recessive deleterious alleles is likely to be the main mechanism of inbreeding depression[1], in addition to inbreeding x environment (IxE) interactions. However, although it is interestingly proposed that future studies using 'omic' technologies will greatly enhance our knowledge of inbreeding effects[2], little mention has been made of the epigenetic chromatin modifications (DNA methylation, histone modifications and RNA interference) that regulate gene transcription during embryonic and subsequent development. There is increasing evidence that epigenetic patterns differ among individuals[3] and that these differences may contribute to part of the natural morphological variation and developmental defects observed in inbred lines[4–7]. Recent research into the contribution of epigenetics to the differential regulation of gene expression, imprinting (a parent-of-origin differential gene expression) and gene silencing, in addition to the involvement of transposable elements in these processes, has shed fresh light on the impact of inbreeding on development.

Epigenetic differences among natural populations and among various ecotypes have been linked to variation in DNA methylation[6,8], and even seem to be directed by small interfering RNAs that match specific genomic regions[9]. It has been clearly established that deficiencies in DNA methylation (mostly CG, but also non-CG in some organisms) are deleterious and lead to early embryo mortality[10,11]. Furthermore, the unmethylated mutants that survive exhibit developmental aberrations of progressive severity as a result of inbreeding[12,13]. It therefore seems that any mutation that leads to the misexpression of genes involved in epigenetic control will have a major effect throughout development and may even lead to diseases in adults, including some tumours. One important step forward in the analysis of epigenetic phenotypic variations is that they can now be estimated in *Arabidopsis thaliana* using recombinant inbred lines, such as 'epiRILs' (epigenetic recombinant inbred lines). These lines are established by crossing a wild-type plant with either a *methyltransferase 1* (*met1*) mutant plant (a null mutant of a maintenance DNA methyltransferase[14,15]) or a *decrease in DNA methylation 1* (*ddm1*) mutant plant (which expresses a mutant chromatin-remodelling protein[6]). Many other lines mutated for various 'epigenetic' genes could therefore help to decipher the impact of epigenetics during inbreeding.

We must consider seriously the impact of epigenetic changes on the phenotypic variation of complex traits — an idea that was initially proposed by Holliday in 1987 (REF. 16) and that has been revitalized by recent observations — and determine the part that inbreeding can play in promoting and revealing this variation. This is relevant because epigenetic and inbreeding effects are sensitive to the environment, which is also known to have a large influence on the regulation of transposable element expression. DNA methylation, DNA-associated protein modifications, chromatin structure and RNA interference — all of which are closely connected epigenetic processes — are therefore crucial for deciphering the underlying genetic causes of inbreeding effects that occur during embryonic development and in adulthood. This should shed new light on an old problem that is still at the forefront of population genetic investigation.

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