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NEWS AND COMMENTARY

Gene expression

Gene expression: an X chromosome look beyond additive and nonadditive effects

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While autosomes spend an equal amount of time in males and females, X chromosomes are unusual in that they reside more often in females. Two-thirds of the X chromosomes in a population will be found in females while the other third will be present in a single copy (hemizygous) in males. Furthermore, X-chromosome hemizygosity makes deleterious or beneficial variation readily expressed and thus subjected to selection in males regardless of its dominance. In contrast, the visibility of a new allele to either positive or negative selection in females will depend on its coefficient of dominance. In a recent paper, Wayne *et al*. (2007) used a classical quantitative genetic cross design to investigate gene expression variation across genotypes within a natural population of the fruit fly *Drosophila melanogaster*. With methods that are well established in the quantitative genetics community, the Wayne *et al*. (2007) study allowed the statistical partitioning of gene expression variation into the classic bins of quantitative genetics: additive and nonadditive variance. Their findings are in good agreement with current theories and highlight a unique contribution that X-chromosome hemizygosity makes toward a simpler mode of gene expression inheritance in males.

First, Wayne *et al*. (2007) found that additive genetic variation is higher on autosomes than on the X chromosome. Lower population sizes of X chromosomes due to male hemizygosity are unlikely to cause this pattern because the large variance in male reproductive success in *Drosophila* may have the net effect of diminishing the differences in effective population sizes of the X chromosome and autosomes. Hence, a more compelling interpretation is that more efficient positive and negative selection on the hemizygous X may underlie its lower levels of segregating variation for alleles with effects on transcription. Finally, Wayne *et al*. (2007) found that males have higher levels of additive genetic variation than females. Accordingly, the number of genes with detectable additive variation was about twofold higher in males, both for autosomal and X-linked genes. Furthermore, approximate measures of the dominance variance indicated no measurable effect in males, whereas females showed a non-negligible effect, with hundreds of genes detected both in autosomes as well as in the X chromosome. Hence, Wayne *et al*. (2007) concluded that gene expression levels are more additive in males, presumably due to the hemizygosity of the X chromosome, which contains some 20% of all *D. melanogaster* genes. While this effect may be particularly strong in fruit flies, it remains to be seen if similar patterns can also be found in organisms with more reduced or gene-poor X chromosomes.

So, in what sense is the mode of inheritance of male transcriptional variation 'simpler'? It is simpler because the lack of diploidy for about 20% of the genome in males results in a much smaller contribution of dominance variation to male expression diversity than to female expression diversity. Hence, in flies, we might expect fathers to be better predictors of their son's expression levels than mothers are to their daughters' expression. It might be worth emphasizing, however, that finding that genetic variation associated with male expression diversity can be predominantly ascribed to the additive component of variation does not imply that male regulatory networks are simpler or less epistatic than those of females. Indeed, from the perspective of regulatory systems, both dominance and epistasis may contribute to additive variance as captured statistically by means of the partitioning of variance components (Cheverud and Routman, 1995). Furthermore, evidence indicates that variation associated with male function and spermatogenesis, in particular, may have complex bases whose large sensitivities to mutational and environmental stresses may even be independent of XY-linkage (Malone and Michalak, 2008).

Studies of additive versus nonadditive variation in gene expression in natural populations have reached seemingly disparate conclusions (Gibson *et al*., 2004; Wayne *et al*., 2004). Two points are worth making here. First, male hemizygosity for the large X chromosome of *Drosophila* may provide one important clue to understanding previous findings. Second, there might be more agreement between studies than is immediately apparent from their distinct emphases on additive and nonadditive variation. Indeed, it would not be surprising if most genes' expression levels are neither purely additive nor purely dominant, but rather have some degree of partial dominance. Unfortunately, measuring degrees of dominance and robustly ascertaining their confidence intervals remain a challenge.

Finally, it will be interesting to see how patterns of differential dominance and additivity of X-linked and autosomal genes may play a role in explaining patterns of sex-biased gene expression, and the masculinization/demasculinization of X chromosomes. Interestingly, while there appears to be a ubiquitous effect of the X chromosome on sex-biased gene expression, the patterns of male- and female-bias of X-linked genes are not universal. In mammals, the X chromosome seems to be enriched in genes fundamental to male function (masculinized) (Khil *et al*., 2004), whereas in fruit flies the X chromosome appears to be depleted of male-biased genes (demasculinized) (Sturgill *et al*., 2007). It remains to be seen how additive and nonadditive gene action of X-linked variation may tie into patterns of sex-biased expression and X-chromosome demasculinization as observed in *Drosophila*.

Gene expression levels offer unique opportunities to understand the mapping of genetic to phenotypic variation. Towards this goal it may be useful to recognize that while in several cases the variation associated with a gene's mRNA abundance may be best described as truly polygenic, there might be many others that are highly skewed toward an oligogenic basis, and a substantial fraction of gene expression differences may be due to a single *cis* or *trans* acting mendelian factor. Eventually, a description of gene expression variation in terms of discrete mutations whose effects cascade through regulatory and protein networks might be achieved, such that the mechanistic and

dynamic regulatory basis of additivity, dominance and epistasis at the level of gene expression can be uncovered.

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