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GENE EXPRESSION

Genetic support network to the rescue

Although great strides have been made in determining individual genotypes, this progress is not matched by a clearer picture of how phenotype follows from genotype. A study in *Caenorhabditis elegans* now shows that the phenotypic consequences of inherited mutations can be accurately predicted by considering variation between individuals in their compensatory responses to the mutation.

The authors' hypothesis was that the variable phenotypic outcome of a mutation is caused by stochastic, inter-individual expression variation in the genetic interaction partners of the mutated gene. To examine this theory, fluorescent transcriptional reporter genes were used to relate gene expression variation during early development to later phenotypes. Specifically, the authors examined variation in the larval phenotype caused by mutations in *tbx-9*, which encodes a T box transcription factor: ~50% of larvae that are homozygous for a null *tbx-9* allele have muscular and epidermal defects, whereas the remainder develop normally. The penetrance of *tbx-9*-null mutations is reduced when *tbx-8*, an ancestral duplicate of *tbx-9*, is experimentally overexpressed. This buffering feedback mechanism was quantified at the expression and phenotypic level in embryos with endogenous levels of *tbx-8* expression: in *tbx-9* mutants, *tbx-8* transcription is upregulated ~1.6-fold in early development, and the degree of this upregulation correlates with the degree of masking of the *tbx-9* mutant defects.

The same phenotypic compensation mechanism was seen between another pair of ancestral gene duplicates: those encoding the zinc finger transcription factors FLH-1 and FLH-2. Together, these two examples support the idea that, in early development, variation in the expression of one gene contributes to the incomplete penetrance of mutations in the other. They also indicate that ancient gene duplicates might be under selective pressure to be retained owing to their canalizing role in development.

However, varying the expression of *tbx-8* does not fully account for the penetrance of the *tbx-9*-null mutations, so the authors considered whether the general buffering mechanisms that are offered by molecular chaperones might account for the rest. The expression of the constitutive chaperone *daf-21* (in the *hsp-90* family) fluctuated among individuals even in wild-type animals. But, as predicted, higher levels of *daf-21* expression correlate with lower penetrance of *tbx-9*-null mutations.

How does the specific and more general mechanism combine to reduce phenotypic penetrance? Expression levels of *tbx-8* and *daf-21* vary independently of each other, but larvae that have high expression both together have the lowest penetrance: 90% of these embryos hatched as phenotypically wild-type larvae.

Therefore, phenotypic outcome does not depend on the intrinsic properties of a mutation but on a range of compensatory mechanisms within the individual. This work provides a general framework for studying the basis of incomplete penetrance and has implications for predicting the consequences of disease-causing alleles.

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ORIGINAL RESEARCH PAPER Burga, A., Casanueva, M. O. & Lehner, B. Predicting mutation outcome from early stochastic variation in genetic interaction partners. *Nature* **480**, 250–255 (2011)