"Nature" Exposes True Phenotypic Effects of Hoxa3D3 Translocations

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One of the greatest scientific breakthroughs in the past decade is the ability to "knockout" and replace genes. These techniques have enabled the scientific community to elucidate the true function of many genes. Hox genes are well known for their role in the early development of the vertebrate body plan. The Hoxa3 locus knockout results in the absence of the thymus gland and leads to fetal lethality. On the other hand, the Hoxb2 locus knockout causes a deformation of the cervical vertebrae, no fatal consequences were observed. This clearly shows that Hoxa3 and Hoxb2 loci separately encode very different functions. Surprisingly, protein sequencing shows 50% genetic dissimilarities, when translocated they perform the same function with no apparent phenotypic effects; this leads us to believe there is some functional overlap within the genes. Early translocation studies done in a laboratory setting using caged mice indicate there is no fitness defect from interchanging these critical development genes. It is surprising to discover that genes with such an important function would still perform efficiently in a completely different role. In order to further analyze these findings we bred Hoxa3D3 homozygotes with mice caught from wild lines, mice that exhibited wild-type behaviors have either the Hoxa3D3 translocation or are wild type at this Hox locus. Competing these two genotypes in semi-natural conditions (i.e., allowing for territorialism, male selection and reproduction to naturally occur) allows us to examine the fitness consequences associated with the Hoxa3D3 translocation. Genotypes from the first 12A6 offspring have exposed a 29% fitness deficiency of the Hoxa3D3 allele (equivalent to a lethal gene with 29% penetrance) indicating this mutation does have a profound effect on fitness. This large drop in fitness is contributed to wild males being 5 times more likely to gain territories (<0.005), resulting in more breeding opportunities. These results indicate Hoxa3 and Hox3D3 alleles are not functionally equivalent and that this ecological competitiveness approach is a key method for understanding the true functions of genes that have no obvious expressed phenotype in laboratory conditions. Ecological competition may prove to be one of the best fitness determinates we currently have at our disposal and is largely ignored when analyzing the fitness of an individual. The work done in our laboratory with Hox gene translocations exemplifies that not all phenotypic observations are accurate and indicates this may be a failure of traditional phenotyping methods.