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New challenges in human genetics: modifier genes

Not all traits are expressed all the time even though the alleles for them may be present. Consistent expression of a phenotype for a given Mendelian trait is fairly rare in higher organisms such as mice and humans. Two well recognized causes for variable phenotypes are the presence of alternative alleles and physiological interaction of environmental factors. A third cause has come to the forefront once again recent studies of mouse genetics, in the form of modifier genes (van Straaten and Copp 2001; Nadeau 2001). These are distinguished from other forms of phenotypic modifiers by studying the same mutant allele in different genetic backgrounds (congenic strains). Instead of masking the effects, a modifier gene modifies the expression of a second gene. The history of genetic modifiers can be traced back all the way to studies on the inheritance of flower colour by Bateson *et al* (1905). Modifier genes influence penetrance, the frequency of expression of an allele (e.g. if 9/10 of individuals carrying an allele express the trait, the trait is 90% penetrant), expressivity (variation in allelic expression from one individual to another) and pleiotropy (the phenomenon where a single gene is responsible for a number of distinct and seemingly unrelated phenotypic effects). There are several examples of modifier effects in mouse and the list is growing in humans (Nadeau 2001; Resendes *et al* 2001; Bala and Peltomaki 2001; Meisler *et al* 2001). Modifier genes seem to offer interesting avenues for an organism to deal with the adverse physiological effects of a genetic mutation by appropriately modulating the biological response processes. Modifier genes discovered in laboratory mice and rats are relevant for studies of human diseases. The mouse genome sequence is expected to accelerate the search for similar modifier genes in the human genome as well, modifier genes whose identification will be important for our understanding of the molecular genetics of human diseases. This is because modifier genes come in two versions: one that modifies the original Mendelian mutant locus positively (disease promoting) and the other negatively (disease suppressing). Unravelling the complex genetic network between Mendelian disease loci and their modifiers in molecular terms will open up ways of countering the problems associated with variable disease presentation and disease therapeutics.

The challenges of molecularly characterizing modifier loci will propel development of newer technologies of extremely high quality for high-resolution mapping and high-throughput genotyping. This may be the only way to comprehend the complex molecular genetics of human diseases.

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