IN BRIEF

EVOLUTION

MHC heterozygosity confers a selective advantage against multiple-strain infections.

Penn, D. J. *et al*. *Proc. Natl Acad. Sci. USA* **99**, 11260–11264 (2002)

Major histocompatibility complex (MHC) loci encode proteins that initiate the clearance of foreign antigens by the immune system. It has long been held that MHC heterozygotes are better at clearing infections, but no proof of this 'heterozygote advantage' theory has been available. Penn *et al*. have now shown that MHC heterozygosity gives mice an advantage in clearing multiple bacterial infections, although, contrary to expectations, the effect is dominant rather than overdominant. This work provides an adaptive explanation for why there is disassortative mating in mice for MHC alleles.

COMPARATIVE GENOMICS

Comparative genomic sequence analysis of the human chromosome 21 Down Syndrome critical region.

Toyoda, A. *et al*. Genome Res. **12**, 1323–1332 (2002)

Toyoda *et al*. report here the largest comparison so far of finished mouse and human sequences. They compared a 1.35-Mb region of mouse chromosome 16 (MMU16) with finished sequence from human 21q22, which might contain a Down Syndrome critical region (DSCR) — believed to contain genes, the altered dosage of which contributes to DS. From this comparison, Yan *et al*. constructed a map that shows all known genes in this MMU16 region, plus 144 conserved regions that don't match known exons. They suggest new structures for previously predicted human genes and importantly compare their results to those produced by two gene-prediction programs, GENSCAN and TWINSCAN.

BEHAVIOURAL GENETICS

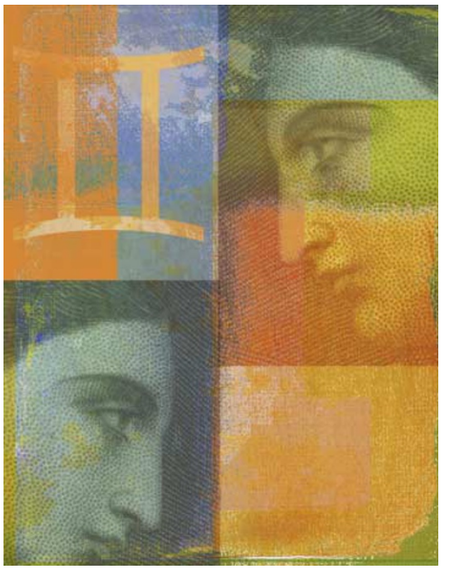
Deficient pheromone responses in mice lacking a cluster of vomeronasal receptor genes.

Del Punta, K. *et al*. *Nature* **419**, 70–74 (2002)

The vomeronasal organ (VNO) is an olfactory organ that detects pheromones. The VNO receptors that detect these chemicals have, until now, remained undefined, but in mice are believed to be encoded by genes in two gene complexes, *V1r* and *V2r*. Here, Del Punta *et al*. report that the deletion of a 600-kb genomic region, which contains a cluster of 16 *V1r* putative receptors genes, alters VNO-dependent behaviours in mutant mice — particularly maternal aggression and male sexual behaviour. These findings, together with the fact that the VNO epithelium of mutant mice is unable to respond to specific pheromonal ligands, confirm that V1r receptors function in pheromone detection.

HUMAN GENETICS

A twin approach to disease



The development of the human lip and palate is a delicate process, requiring tissues from both sides of the face to migrate and meet neatly in the middle. It is therefore not surprising that cleft lip and palate, in which this process goes awry, is relatively common — it affects 1 in 700 newborns — and can be caused by either genetic or environmental influences. In an inventive and thorough study, Kondo and colleagues now identify the causative gene of two common cleft lip or palate disorders.

The two syndromes in question — Van der Woude (VWS) and popliteal pterygium (PPS) — are characterized by cleft lip and palate, with PPS individuals also sufferring from skin and genital abnormalities. It had been suspected that the two disorders are allelic, and that they mapped somewhere in the 1q32–41 interval. This was confirmed when the authors sequenced the candidate region in a pair of identical twins that were discordant for the VWS phenotype. The only genetic difference was a nonsense mutation in the interferon regulatory factor 6 (*IRF6*) gene, which belongs to a family of nine transcription factors. *IRF6* mutations were also found in 57 other families with either VWS or PPS; the causative role of *IRF6* in VWS and PPS was further supported by the high expression of *IRF6* in the tissues that are affected in the two disorders.

The two syndromes might be allelic but they are characterized by a different spectrum of mutations in the functional regions of *IRF6*: VWS-associated mutations map to both the DNA-binding and dimerization domains, whereas lesions in PPS patients affect only DNA-binding residues. These lesions could explain the dominant nature of VWS and PPS: the common, protein-truncating mutations seen in VWS are probably haploinsufficient null alleles, whereas the PPS mutant proteins have a dominant negative effect, as they retain the ability to bind protein partners but not DNA.

This work provides proof of principle that identical twins can be used to pinpoint disease genes, an approach that removes the complicating presence of neutral SNPs. Nonetheless, mutations in *IRF6* don't explain everything, as phenotypic variation in VWS and PPS patients betrays the presence of modifier genes and/or random effects.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Kondo, S. *et al*. Mutations in *IRF6* cause Van der Woude and popliteal pterygium syndromes. *Nature Genet.* 3 Sep 2002 (doi:10.1038/ng985)