# IN BRIEF

COMPARATIVE GENOMICS

### A genetic linkage map of the baboon (*Papio hamadryas*) genome based on human microsatellite polymorphisms.

*Rogers, J.* et al. Genomics ***67****, 237–237 (2000).*

This is the first non-human primate linkage map, in which 694 baboons were genotyped for 325 human and six novel baboon microsatellite markers across all 20 baboon autosomes. Locus order on seven human chromosomes was found to be conserved when the baboon and human maps were compared, and centiMorgan distances indicate that recombination rates are higher in humans than in baboons.

DISEASE MODEL

### A novel genetic pathway for sudden cardiac death through defects in the transition between ventricular and conduction system cell lineages.

*Nguyen-Tran, V. T. B.* et al. Cell ***102****, 671–682 (2000).*

By inactivating *HF-1b*, a transcription factor gene that is preferentially expressed in the heart, these researchers generated the first mouse model of sudden cardiac death. Although the mutant mice survive to term and their hearts develop and function normally, they die suddenly at 1–6 months of age from ventricular arrhythmias. The altered expression patterns of conduction system-specific markers indicate that cells of the ventricular muscle and conduction system fail to differentiate with normal electrophysiological properties.

ASSOCIATION STUDIES

### The common PPARγ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes.

*Altshuler, D.* et al. Nature Genet. ***26****, 76–80 (2000).*

The authors evaluated 16 published genetic associations to type 2 diabetes. Only one significant association to a decreased risk of diabetes type 2 was confirmed. This was with a common Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-γ gene, which encodes a nuclear hormone receptor that regulates adipogenesis. The common proline allele has a modest effect on individual risk but influences up to 25% of type 2 diabetes in the population.

HUMAN MUTATION RATE

### Estimate of the mutation rate per nucleotide in humans.

*Nachman, M. W.* et al. Genetics ***156****, 297–304 (2000).*

This paper provides a precise estimate of the rates and patterns of human mutations at the nucleotide level (reviewed in this issue by Jim Crow). By sequencing 18 processed pseudogenes in humans and chimpanzees, the authors estimate that 175 new mutations occur per generation, with mutations at CpG dinucleotides occurring ten times more frequently than at other sites. The mutation rate in males is four times higher than that of females, but no differences were seen between sex chromosomes and autosomes.

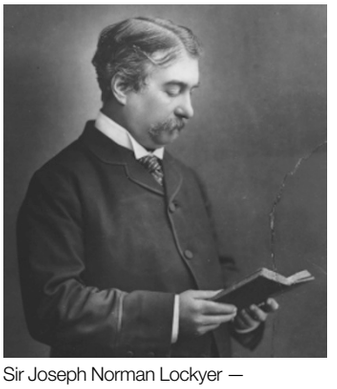
IMMUNOGENETICS

# Not just another editor

Our immune system uses some fascinating genetic mechanisms to generate the huge diversity of antibodies necessary to fight infection — combinatorial diversity, class-switching and somatic hypermutation. And now RNA editing can be added to the list.

Antibody genes are assembled from DNA segments (V, D and J) by site-directed recombination: because there are many copies of each segment, this generates combinatorial diversity. Class-switching swaps a segment encoding the constant region of the antibody for another segment. This alters the functionality of the antibody — changing an IgM antibody to an IgG antibody, for example. The antibody is then finely tuned by somatic hypermutation. As the antibody gene is expressed in maturing B cells, mutations are generated at high frequency and the antibodies with the highest affinities for antigen are selected.

As far as the mechanisms are concerned, quite a bit is known about V(D)J recombination, but we know little about the molecules responsible for class-switching and somatic hypermutation. In previous work, Tasuku Honjo and colleagues have used a cell-based assay to look for genes expressed during class-switching and identified a new RNA editing enzyme known as activation-induced cytidine deaminase (AID). In the latest work, gain-of-function and loss-of-function analyses establish a clear role for AID in class-switching and somatic hypermutation.



Sir Joseph Norman Lockyer — the founding editor of *Nature*.
Courtesy of Hulton-Deutsch Collection/CORBIS.

Muramatsu *et al.* have shown that increased expression of *AID* can induce class-switching in the cell-based assay. Furthermore, when they knocked out *AID*, the homozygous mice lost all class-switching. The authors also assayed for hypermutation and found a tenfold reduction in mutation rate in mutants, relative to wild-type littermates.

In an accompanying paper, Revy *et al.* present the human story. They mapped an autosomal recessive form of an immune abnormality known as hyper IgM syndrome, and by a positional candidate approach, they found that the human *AID* gene carries causative mutations in 12 families. Like the knockout mice, *AID* deficient humans have no class-switching and severely reduced hypermutation. The evidence is watertight — AID is necessary for class-switching and somatic hypermutation.

But how does an enzyme that changes C's to U's in RNA transcripts contribute to antibody diversity? At this stage, it is only possible to speculate. The closest homologue to AID is the RNA editing enzyme, APOBEC1, which has one specific target — the apolipoprotein B transcript. Does AID just modify the transcript of one gene, leading to the synthesis of a protein that plays a specific role in switching and hypermutation? Or, does AID have multiple targets? Whatever they are, antibody gene expression has just become even more interesting, and like Lockyer back in 1869, AID is one editor we couldn't do without.

*Mark Patterson*

**References and links**

**ORIGINAL RESEARCH PAPERS** Muramatsu, M. *et al*. Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme. *Cell* **102**, 553–563 (2000). | Revy, P. *et al*. Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the hyper IgM syndrome (HIGM2). *Cell* **102**, 565–575 (2000).

**FURTHER READING** Longacre, A. *et al*. A novel cytidine deaminase affects antibody diversity. *Cell* **102**, 541–544 (2000)