Breaking laws and obeying rules

Sir — In the excitement of breaking Ohno's Law and trying to explain Haldane's rule, I think we might have overlooked the real significance of the finding that a gene has been lost from the X chromosome in the laboratory mouse as reported in the August 1995 issue of *Nature Genetics*[1],[2]. After all, it is hardly the first violation of Ohno's Law. Earlier this year, it was demonstrated that steroid sulphatase (*STS*) and *ANT3*, which lie within or near the pseudoautosomal region (PAR) of the human X, are autosomal in lower primates[3]. In fact, exemption from Ohno's Law had to be granted ten years ago for two of the three major groups of extant mammals when, as Ellis[4] points out, it was discovered that almost the entire human Xp (not just a gene or two) is missing from the X in both marsupials and monotremes. Dr. Ohno, when I visited him to confess to this major transgression, was not upset in the least. Indeed there is a good explanation in the hypothesis that the human Xp region was recently added in bits to the PAR shared by an ancient X and Y, then progressively degraded on the Y, the homologous region being recruited into the inactivation system on the X[5]. This attrition left a small and ever-dwindling X–Y homologous 'pseudoautosomal' region (PAR) which was boosted now and then by autosomal additions.

The new finding that the chloride channel gene, *Clcn4*, is on the X in *Mus spretus* but is autosomal in *M. musculus* says more about its evolutionary history than its present day function, and I contend that both mouse species have behaved in a perfectly Lawful manner. Pseudoautosomal genes are exempt from Ohno's Law because they have active partners on the Y and are not subject to inactivation. Exchanges involving the PAR do not disrupt X inactivation, and are less stringently selected against than exchanges involving the differential region. Comparative mapping data imply that *Clcn4*, as well as *Sts*, and *Amg*, was part of a region which was originally autosomal in a therian ancestor (and still is in marsupials and monotremes), but was moved to the X and Y early in the eutherian radiation to enlarge an ancestral PAR.

I propose that the *Amg–Clcn4–Sts* region was still pseudoautosomal in the common ancestor of *M. spretus* and *M. musculus* three million years ago (Fig. 1). In the *M. spretus* lineage, the region between *Amgx* and *Sts* was lost from the Y and recruited into the X inactivation system, imposing strict conservation in compliance with Ohno's Law. In the *M. musculus* lineage, however, the region was translocated from the PAR to an autosome, which is also a perfectly Law-abiding event. Translocation from an ancient PAR can equally well account for the autosomal location of *Csf2ra* and *Il3ra* in mouse, and of *STS* and *ANT3* in prosimians.

These changes in location of *Clcn4* still involve changes in gene dosage, but they are the other way around from those which were proposed. In the above hypothesis, the two *Clcn4* copies on *M. musculus* chromosome 7 simply maintain the ancestral autosomal, then pseudoautosomal, condition. However, the loss of an active allele from the Y and the recruitment into the inactivation system on the X has reduced the dosage of active Clcn4 copies from 2 to 1 in *M. spretus* (as well as human and rat). Although the dosage of this gene does not seem to matter very much in the short term, since even nullisomics are viable, it will be of great interest to determine whether halving of gene dosage has selected for changes in level of expression over the last few million years.

Lastly, I do not see how non-homology around the *Clcn4* gene can explain the phenotype of *M. spretus* × *M. musculus* hybrids, which also obey Haldane's Rule that interspecific males are often sterile. It is hard to see why non-homology would disrupt X–Y pairing and cause male sterility unless the breakpoint of the rearrangement interrupts the present PAR, which apparently it does not. It certainly would have disrupted the larger ancestral PAR, and may have been involved in the original speciation event. However, I wish that geneticists would look a little beyond mouse before deciding on a general explanation for Haldane's Rule. The Law-breaking marsupials do obey Haldane's Rule, although there is evidently no PAR shared between the small, completely differentiated X and Y chromosomes. Many years of working on comparative genome mapping has convinced me that mouse is a marvellous model for some things but its genome arrangements and rearrangements may be, well, very mousey.

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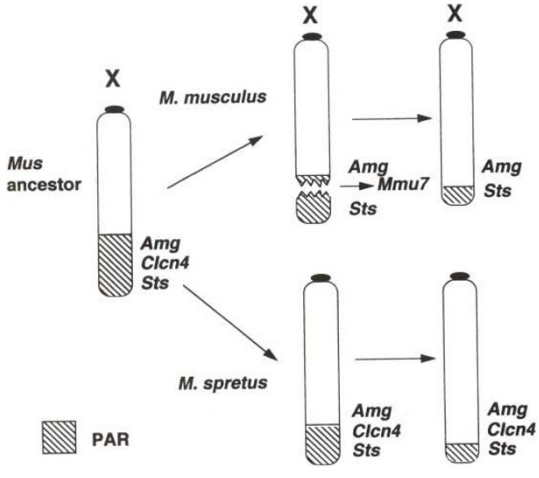

Fig. 1 Arrangement of the terminal *Amg–Clcn4–Sts* region on the mouse X. In the ancestral *Mus* species, the pseudoautosomal region extended proximally from the telomere and included *Sts*, *Clcn4* and *Amg*. In the *M. spretus* lineage, the regions containing first *Amg*, then *Clcn4*, were lost from the Y and recruited to the inactivation system on the X to leave *Amg* and *Clcn4* as part of the differentiated region of the X. In the *M. musculus* lineage, however, the *Clcn4* region was translocated from the ancestral PAR onto chromosome 7.

Reply — The molecular events underlying the evolution of species are hard to predict. Attempts to draw the evolutionary history of everyone's favorite species may result in fascinating tales; however, scientists should stick to the facts. Namely that a gene, *Clcn4*, was discovered to be located on the X chromosome in one mouse species and on an autosome in another[1,2]. This unprecedented finding in the mouse has obvious implications to both Ohno's law and Haldane's rule. Whether or not it represents an exception to Ohno's law or it obeys Haldane's rule depends on how strictly Ohno's and Haldane's original thoughts are interpreted. I