nature genetics

A high-wire act

"Every second, in return for their two hundred thousand billion global sperm, [men] are rewarded with five births. The world's women contribute a mere four hundred eggs with each tick of the clock for the same result."

—Steve Jones, Y: The Descent of Men

Being male is a risky strategy, and being the chromosome that determines maleness likewise incurs hazard. Since the human Y chromosome was identified (*Science* **53**, 503–504; 1921), its reputation has careened from extreme to extreme. Renown peaked for the Y chromosome as the bearer of the gene *SRY* encoding the testis-determining factor: dominant, necessary and sufficient for testes, and thus for male, development (*Nature* **346**, 240–244; 1990 and *Nature* **351**, 117–121; 1991). At other times, the Y has been variously viewed as a genetic badlands of repetitive redundancy, in irreversible decay, eroding towards extinction (*Phil. Trans. Roy. Soc. Lond. B* **355**, 1563–1572; 2000). The male chromosome's honor has been restored in the light of a wealth of new information (accessible from a Nature Web Focus at http://www.nature.com/nature/focus/ychromosome). The way this has happened provides several instructive examples of synthesis, the process whereby inconsistent opposing hypotheses are reconciled to generate conceptual advances.

Part of the male-specific region of the Y chromosome (MSY), the *AZFc* neighborhood, comprises repeats called amplicons that are each hundreds of kilobases in length (*Nat. Genet.* **29**, 279–286; 2001). The genes residing in the amplicons are predominantly expressed in testes, where they probably function in spermatogenesis. Interspersed among the amplicons are X-degenerate sequences related to genes carried on the X chromosome. Without meiotic recombination, most of these have degenerated to pseudogenes, but 16 coding genes have clung to their slippery perch (*Nature* **423**, 825–837; 2003).

The first contradicting observation is that the MSY doesn't recombine with a homolog because it has diverged too far from the X. Opposed to this is the idea that Y must have some recombinational mechanism or it would succumb to the accumulation of deleterious mutations. The synthetic answer—and a genetic reprieve for the Y—comes in the form of intrachromosomal gene conversion acting to conserve the function of testis-specific genes in the euchromatic male-specific region of the chromosome by copying in the sequence of a matching repeat (*Nature* **423**, 825–837; 2003).

Second, in the absence of contrary evidence, the Y has been considered evolutionarily neutral. Opposing this view, it also rapidly accumulates deletions. This mutational pressure ought to result in high population frequencies of deleted Y chromosomes. In this issue, we publish the synthesis that resolves that problem. On page 247, Sjoerd Repping *et al.* report a frequently recurring Y chromosome deletion that is maintained as a polymorphism at a frequency much lower than the neutral prediction of 40%. Because the deletion is in a region of the Y required for spermatogenesis, the authors propose that the deletion confers a selective disadvantage, and they demonstrate an associated increase in risk of infertility. The population frequency is consequently the product of opposing mutation and selection. As Chris Tyler-Smith and Gil McVean point out in the accompanying News and Views on page 201, this work deprives population geneticists of one of their favorite neutral loci but clears the way for studies of Y chromosome function.

Third, some Y deletions are sterile (*Nat. Genet.* **29**, 279–286; 2001). Conversely, some deletions of MSY 'spermatogenesis genes' are not. These competing observations may be resolved by the observation of Sjoerd Repping *et al.* that at least some MSY deletions are accompanied by compensatory duplications. Thus, rather than inexorably whittling the male sex chromosome down to an evolutionary dead end, recombination may sometimes be an important means of generating sequence redundancy, acting in concert with the extreme sampling and selection that male gametes undergo (see quote above) to promote diversification and to enable production of more fit gametes.

These recent discoveries show that the male chromosome may be far more functional, flexible and versatile than we have given it credit for. Nevertheless, the casting and recasting of its roles that it has endured has been a productive process. This is because the reconciliation of opposing extreme views will often give birth to a new model capable of accommodating the original observations. In the case of the Y, this restoration of balance is welcome because it indicates a secure way forward in the quest for the functions that it carries. ■