

tions in methylation and chromatin structure, illustrating how changes in epigenetic regulation can spiral out of control towards genomic instability. ■

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Evolutionary genomics

Sex and the X

Laurence D. Hurst

Are genomes made up of strings of genes in no particular order? It seems not, given the abundance on the mouse sex chromosomes of genes involved in the manufacture of sperm.

It is often presumed that there is no relationship between what a gene does and where it is in the genome. Nonetheless, there are more genes involved in the manufacture of sperm (spermatogenesis) on the mammalian Y chromosome than might be expected by chance¹. Now, writing in *Nature Genetics*, Wang *et al.*² describe how they identified 25 genes involved in spermatogenesis in mice and found that they are over-represented on both the X and Y chromosomes. This finding adds to the growing realization that genes on the X and Y chromosomes are commonly involved in the development of differences between the sexes.

This might at first sight appear self-evident. Indeed, the mammalian gene that makes males male (*Sry*) must be Y-linked as its presence defines the Y chromosome. Likewise, genes might be on the Y chromosome simply as a convenient way of ensuring that they are expressed only in males. But it is not at all obvious why a gene that is expressed only in males need be on the X chromosome. Something must act to turn the gene on only in males, whether on the X chromosome or on an autosomal (non-sex) chromosome. Given the presence of such a switch mechanism, what is gained by having the gene on the X rather than on an autosome? That the X chromosome might contain an excess of genes that are sex specific in their expression was predicted almost 20 years ago³, however.

To isolate the genes involved in spermatogenesis, Wang *et al.*² used a subtraction method. The cells they looked at were spermatogonia, which are found in the testis and are involved in the early stages of sperm production. These cells have a full complement of genes, as opposed to the half-

complement found in sperm themselves. In these experiments a sample of gene transcripts from spermatogonia was depleted of transcripts shared with non-germline cell types. Wang *et al.* then determined the DNA sequence of the residual, spermatogonia-specific transcripts. They identified a total of 36 genes, including all of the eight previously known to be expressed exclusively in spermatogonia. Of these 36 genes, 25 were confirmed to be expressed in spermatogonia only; the remaining 11 made for an informative comparison sample of genes, as they were expressed in both male and female germ cells.

Where are these genes in the genome? The two sets told different stories. Of the 11 that are expressed in both sexes, one is X-linked and ten are on the autosomal chromosomes. Nothing unusual there. By contrast, 10 of the 25 spermatogonia-specific genes are X-linked and three are Y-linked (Fig. 1). If the 22 non-Y-chromosome, spermatogonia-specific genes were randomly distributed, then we would expect only about one to be X-linked.

This finding has at least one ramification. Sometimes, in both mammals and fruitflies, matings between different species result in normal daughters but sterile sons. Many of the hybrid sterility genes are X-linked⁴ but quite why is a matter of contention. That the X chromosome contains so many genes involved in the manufacture of sperm must now be considered as a likely component of the explanation.

More generally, the finding accords with other studies that suggest that X-linked genes are commonly involved in determining the differences between the sexes. For example, analysis of human disease mutants reveals that a gene locus on the X chromosome is at least three times more likely to be involved in sexual development than is a locus on an autosomal chromosome⁵. Similarly, the average influence of X-linked genes on features that are used by males to attract females is much larger than the average influence of X-linked genes on other traits⁶.

This general result, that sex chromosomes harbour many sex-related genes, was predicted by Rice³. He considered the fate of 'sexually antagonistic' alleles — that is, different forms of the same gene that are good for one sex but bad for the other. An example could be an allele that makes individuals brightly coloured. This may benefit males by

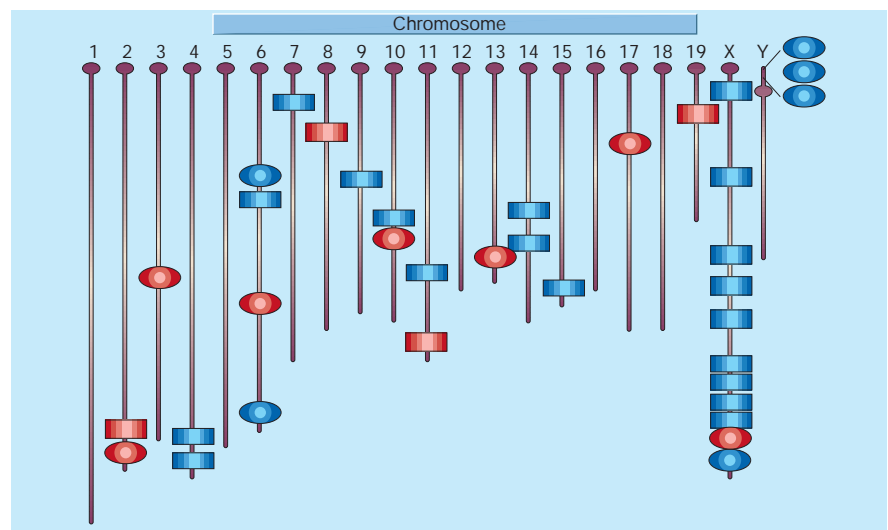


Figure 1 Location in the mouse genome of 36 genes active during sperm production. Genes in blue are expressed in the spermatogonia (male germ cells) only; those in red are expressed in the ovary (female germ cells) as well. Wang *et al.*² find that the spermatogonia-specific genes are heavily concentrated on the X chromosome (10 out of 25). Previously known genes are shown as ovals, and those newly identified by Wang *et al.* as oblongs. (Modified from ref. 2.)

making them conspicuous (and attractive) to females, but is disadvantageous to females as it simply increases the chance that predators will detect them.

Consider what will happen to an initially rare recessive allele that is beneficial to males (the XY sex) but deleterious to females (the XX sex). If it is located on the X chromosome, the allele is very likely to increase in frequency, even if the benefit to males is considerably less than the cost to females. This is because in the XY condition, the beneficial effects are evident, whereas in females the detrimental effects are masked when the allele is rare. By contrast, the allele is unlikely to increase in frequency if it is on an autosomal chromosome, for two reasons. First, because it is recessive, its effects would be hidden. Second, even if they are not perfectly hidden, the net advantage to the males must outweigh the net detriment to the females. The X chromosome therefore acts, overall, as a filter for sexually antagonistic alleles.

Furthermore, as the allele on the X chromosome rises in frequency in the population, some females will carry two copies of it. In this condition the effects of the allele will not be masked and will be detrimental to females. Natural selection should then favour abolition of its expression in females³. Rice's model therefore makes good sense of the fact that genes expressed exclusively in male germ line are predominantly X linked, but those expressed in both sexes are not.

The model can also make sense of the accumulation^{1,2} of spermatogenesis genes on the Y chromosome. In this case, the argument is that, because Y-linked genes occur exclusively in males, negative effects in females need never be realized. Such a mechanism could also explain⁷ why, in guppies, many of the genes for male-specific traits (such as coloration) that females find attractive are on the Y chromosome⁸.

Numerous uncertainties remain, however. Rice's model proposes that the spermatogenesis genes on the X chromosome evolved their function and male-specific expression after becoming X-linked. But could it be the other way around: could genes be more likely to become X-linked, possibly by chromosomal translocation, because they are ancestrally sexually antagonistic⁹? Analysis of the expression of the same genes in non-mammalian vertebrates could resolve the issue. Further, muscle-specific genes¹⁰ are especially abundant on the X chromosome, whereas placentally expressed ones¹¹ are unusually rare. It is not clear why¹².

These uncertainties aside, it is becoming clear that genomes are not the randomly arranged set of genes that we might have imagined them to be. But is this also true at a smaller scale? For example, could natural selection explain which genes are next to each other on a given chromosome? The clustering of broadly expressed genes¹³,

such as those for the everyday running of cells, suggests that small-scale gene arrangements are not always random. These could be exceptions rather than the rule, however, and clarification of the issues awaits the sequencing of the complete genomes of more organisms. ■

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Earthquakes

Shock delay

Elizabeth Harding Hearn

Postseismic stress transfer is the local redistribution of stresses in the Earth's crust that follows an earthquake. It's a hot topic at the moment, and understandably so because of its relevance in assessing seismic hazards.

The magnitude-7.1 Hector Mine earthquake occurred only about 20 km from the site of another large earthquake in southern California, but happened seven years later. Were the two connected? On page 180 of this issue¹, Freed and Lin describe their investigations into the question.

Earthquakes change stresses in the surrounding Earth's crust, so it is not surprising that the initial jolt of a major earthquake is followed by a sequence of aftershocks that (fortunately) decay with time. Aftershocks tend to occur on faults where the 'shear stress' (τ) loading the fault has increased or the 'compressive stress' (σ) clamping the fault has decreased, or both². The Hector Mine earthquake of 1999 did not seem to fit into this picture: it occurred geographically close to, but seven years after, the magnitude 7.3 Landers earthquake, and in an area where most researchers consider that the change in stress after Landers should not have encouraged seismic activity.

Freed and Lin¹ now show how post-seismic deformation — continued deformation of the Earth's crust during the years after the Landers earthquake — may have increased stresses at the hypocentre of the Hector Mine earthquake and triggered that event. Their modelling study shows that, within a few years of an earthquake, post-seismic deformation may change stresses in the upper crust by at least as much as the stress released by the earthquake itself. The study shows, too, that estimating such changes is crucial for characterizing regional seismic hazards.

Seismologists have been fairly successful at explaining the spatial² and temporal³ distribution of aftershocks using models that account only for the stress changes occurring

during an earthquake (coseismic deformation). According to these models, an interplay between the Coulomb stress (τ minus a scaling constant times σ) and the time-dependent evolution of frictional properties of faults explains how an earthquake can trigger other earthquakes within about a hundred kilometres for days to months after the main shock. But sustained postseismic deformation is required to explain the triggering of aftershocks that occur several years after a large earthquake. If the entire crust were effectively elastic (that is, it did not undergo distributed deformation over time following a coseismic stress change), any broadly distributed postseismic deformation would probably be due to sliding of faults at depth^{4,5}. But the lower crust and upper mantle are viscoelastic materials that cannot support significant shear stresses and tend to yield with time. After an earthquake, the lower crust gradually relaxes its grip on the upper crust, allowing the upper crust to continue deforming in a directional sense comparable (in most areas) to the coseismic deformation.

Freed and Lin¹ propose that viscoelastic relaxation of the lower crust⁶ continuously increased the Coulomb stress at the Hector Mine hypocentre, until it exceeded a threshold and triggered the earthquake. They find that the postseismic Coulomb stress change at the hypocentre was about 1 bar, which is several times the most generous published estimate of coseismic Coulomb stress⁷. Viscoelastic relaxation efficiently transmits post-seismic stresses to great distances, so Freed and Lin's model also suggests that the Landers earthquake has resulted in considerable changes in stress on other active faults in southern California, such as the San Andreas.