Evolution

A chromosome predisposed for sex

Yuying Lin & Judith E. Mank

A genome sequence for the flatworm *Schmidtea mediterranea* reveals a chromosome that might be primed to become a sex chromosome. The finding offers a remarkable chance to study the evolution of sex determination. **See p.329**

There is an interesting dichotomy in the fact that sperm and eggs are broadly similar across animals, and yet the mechanism by which sex is determined varies enormously[1]. For instance, some animals are hermaphroditic, producing both eggs and sperm, either simultaneously or sequentially. Many other animals spend their entire lives as either females or males. In this case, sex can be determined by ecological factors such as temperature or demography, or by sex chromosomes. This diversity makes sex determination challenging to understand – a problem compounded by the fact that sex-determination mechanisms often evolve rapidly, and can vary even between closely related species[2]. On page 329, Guo *et al.*[3] offer clues to how animals might transition from hermaphroditism to having separate sexes using sex chromosomes, with an unexpected twist to events.

The evolution of sex chromosomes has puzzled researchers since 1905, when the geneticist Nettie Stevens first described these chromosomes in meal worms[4]. It has become clear that, despite having arisen independently many times in plants and animals, sex chromosomes generally have similar key characteristics[5], most notably a male-limited region on the Y chromosome that contains at least one sex-determining gene crucial for male gonad development. Most chromosomes exchange material through a process called recombination during the meiotic cell divisions that form sperm and eggs. By contrast, the male-limited region of the Y chromosome has stopped recombining with the other member of its pair, the X chromosome.

Theoretical models posit that a sex-determining gene that directs testis development emerges first on an otherwise normal chromosome, and recombination is then suppressed in the chromosomal region around it[6]. As recombination suppression evolves, the Y chromosome becomes isolated from the X, and so X and Y chromosomes slowly become more and more different from one another (Fig. 1a). The non-recombining portion of the Y chromosome, often referred to as a haplotype, is inherited as a single unit from father to son.

Guo *et al.* present a different order of events. Studying the genome of the hermaphroditic flatworm *Schmidtea mediterranea*, the group observed two large haplotypes, named J and V, on different copies of chromosome 1. In individuals with one copy of each haplotype (heterozygotes), the two copies of chromosome 1 form a ring during meiotic cell division, connected and recombining only at the ends. The J and V haplotypes, which make up the central portion of each chromosome, do not recombine with each other, just as the X and Y chromosomes do not recombine. Also like the X and Y, the *S. mediterranea* haplotypes are genetically distinct from one another in both DNA sequence and the expression of many genes.

Non-recombining, genetically diverged haplotypes are not uncommon in genomes, but what is unusual about the *S. mediterranea* haplotypes is that the region contains many of the genes that underlie both male and female gonad development. It could easily be imagined that just a few mutations in these genes could produce a haplotype that is necessary for one sex. For instance, a mutation in one haplotype that prevents expression of a gene essential for ovary development would make that haplotype male-determining, similar to the Y chromosome. The organism would then begin the transition from being hermaphroditic to having two separate sexes, determined by sex chromosomes.

For *S. mediterranea*, then, the events that might lead to the evolution of sex chromosomes started with the arrest of recombination, followed by the divergence of haplotypes. For sex-chromosome evolution to progress, one haplotype must go on to

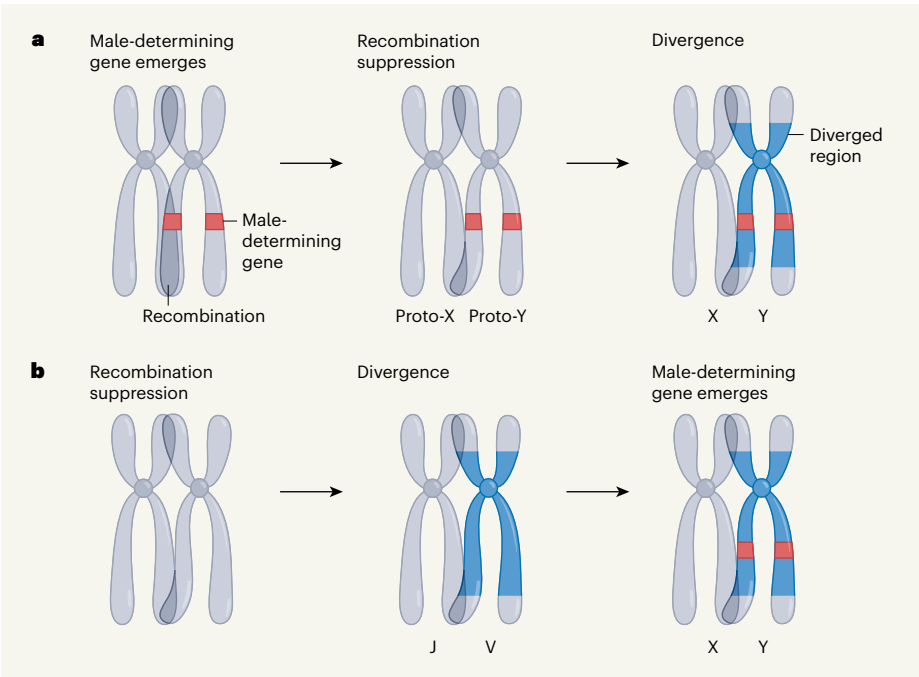

Figure 1 | Two routes to sex chromosomes. a, Chromosomes exchange genetic material through recombination (indicated by overlapping regions) during the cell divisions that produce eggs and sperm. The conventional model of X–Y sex-chromosome evolution posits that a gene that directs development of male embryos emerges on one chromosome, and that – over evolutionary timescales – recombination is suppressed around the gene, ensuring that it is always inherited from father to son as part of a proto-Y chromosome. Finally, the Y chromosome diverges from the other member of its pair, dubbed X. **b**, Guo *et al.*[3] propose an alternative model of sex-chromosome evolution for the flatworm *Schmidtea mediterranea*. First, two versions of chromosome 1 stop recombining, apart from at their tips. After this, one diverges from the other to make two different 'haplotypes' (dubbed J and V). Finally, the male-determining gene emerges on one haplotype, and X and Y chromosomes are formed.

become sex-specific through the emergence of a sex-determining gene (Fig. 1b). This is different from the standard model for the evolution of sex determination, but if we have learnt anything about sex-chromosome evolution, it is that there are multiple evolutionary routes[7] and no single model explains them all.

The *S. mediterranea* haplotypes potentially offer a remarkable system for studying the genes involved in the evolution of sex determination. Interestingly, Guo and colleagues propose that a fully hermaphroditic species has a region of the genome that is predisposed to being a sex chromosome, with no apparent evolutionary reason for it. What we do not know, however, is whether this region would actually become a sex chromosome. It might or it might not, and there are many sex-determining genes on other chromosomes that could evolve into sex chromosomes through the conventional model.

In support of the idea that chromosome 1 can evolve into a sex chromosome, the authors point to evolutionary conservation of gene content between the chromosome 1 haplotypes and the sex chromosomes in a distant relative, *Schistosoma mansoni* – the only flatworm for which a full genome sequence that has sex chromosomes is available. Broader comparative work could determine whether these haplotypes comprise sex chromosomes in other species. Genetic manipulation of the haplotypes in *S. mediterranea* could also be used to engineer chromosome 1 to become proper sex chromosomes. Such avenues offer exciting ways to determine the prevalence and mechanism of this route to sex determination.

Yuying Lin and **Judith E. Mank** are in the Department of Zoology and Biodiversity Research Centre, University of British Columbia, Vancouver V6T 1Z4, Canada. **J.E.M.** is also in the Centre for Ecology and Conservation, University of Exeter, Penryn, UK.
e-mail: judith.mank@ubc.ca

1. Bachtrog, D. *et al. PLoS Biol.* **12**, e1001899 (2014).
2. Beukeboom, L. W. & Perrin, N. *The Evolution of Sex Determination* (Oxford Univ. Press, 2014).
3. Guo, L. *et al. Nature* **606**, 329–334 (2022).
4. Stevens, N. M. *Studies in Spermatogenesis with Especial Reference to the "Accessory Chromosome"* (Carnegie Inst. Wash., 1905).
5. Wright, A. E., Dean, R., Zimmer, F. & Mank, J. E. *Nature Commun.* **7**, 12087 (2016).
6. Charlesworth, B. *Science* **251**, 1030–1033 (1991).
7. Furman, B. L. S. *et al. Genome Biol. Evol.* **12**, 750–763 (2020).

The authors declare no competing interests.
This article was published online on 1 June 2022.

Nuclear physics

Diverse data tighten neutron-star constraints

Jorge Noronha

Analysis of data from astrophysical and terrestrial sources offers a promising way of narrowing the range of parameters that describe the extreme properties of neutron stars. **See p.276**

When two neutron stars spiral into each other, the object that results from their merger has an inner density that can be several times the density of an atomic nucleus (itself around 10 trillion times that of solid gold) and a temperature of around 100 billion degrees Celsius. Such events can therefore offer key information about the properties of matter at extreme densities and temperatures. However, the equations that describe ultradense matter cannot be solved exactly, and current numerical techniques cannot yet approximate the dense environment of a neutron star[1]. Progress in understanding these properties therefore requires collaboration between scientists in different fields, and assimilation of different types of data. This 'big science' approach is showcased to great effect on page 276, where Huth *et al.*[2] report a comprehensive analysis of neutron-star matter using astrophysical observations, experiments on heavy-ion collisions and nuclear-physics models.

Quantum chromodynamics is the fundamental theory that describes the subatomic particles called quarks and gluons, and their interactions. As such, the theory describes nuclear matter, and it gives rise to the nuclear equation of state, which governs the behaviour of the dense matter found in neutron stars. For example, the equation can reveal how the neutron stars' pressure varies with density and temperature. Theories developed to approximate quantum chromodynamics can account for matter with densities up to twice that of a nucleus, but above this value, the nuclear equation of state can be only constrained – not calculated exactly – using input from experiments and observations.

Some of the observations that Huth and colleagues considered came from a binary neutron-star merger that was first identified on 17 August 2017 through detection of the gravitational waves it had produced[3]. The discovery sparked a worldwide observing campaign in the hours and days that followed, resulting in the detection of many electromagnetic signals that were consistent with the radiation expected from the merger. This event heralded the dawn of the 'multi-messenger' astronomy era.

Whereas theory can determine the equation of state for matter at and below nuclear densities, these astrophysical observations proved crucial for inferring the parameters relevant for high densities. And Huth *et al.* found that data from experiments on collisions between gold nuclei had a pronounced impact on the nuclear equation of state at densities around 1.5 times that of a nucleus (Fig. 1). These data, which came from two experiments[4,5] performed in a synchrotron ion accelerator at the GSI Helmholtz Centre for Heavy Ion Research in Darmstadt, Germany, effectively bridged the gap between theory and astrophysical observations.

Huth *et al.* used Bayesian inference to combine all of these data with the theory in

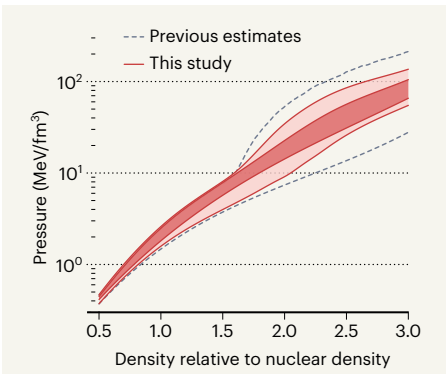

Figure 1 | Constraining the physics of neutron-star matter. Huth *et al.*[2] combined data from astrophysical observations and ion-collision experiments to improve estimates (with 68% and 95% confidence; red and pink shaded areas, respectively) of the parameters in the equation that describes the high-density environment of a merger of two neutron stars. The combined data were crucial for constraining parameters such as pressure (in megaelectronvolts per fm^3, where 1 fm is 10^{-15} m) above densities of around 1.5 times that of a nucleus, at which current nuclear-theory calculations become more uncertain than they are at nuclear densities. (Adapted from Fig. 1d of ref. 2.)