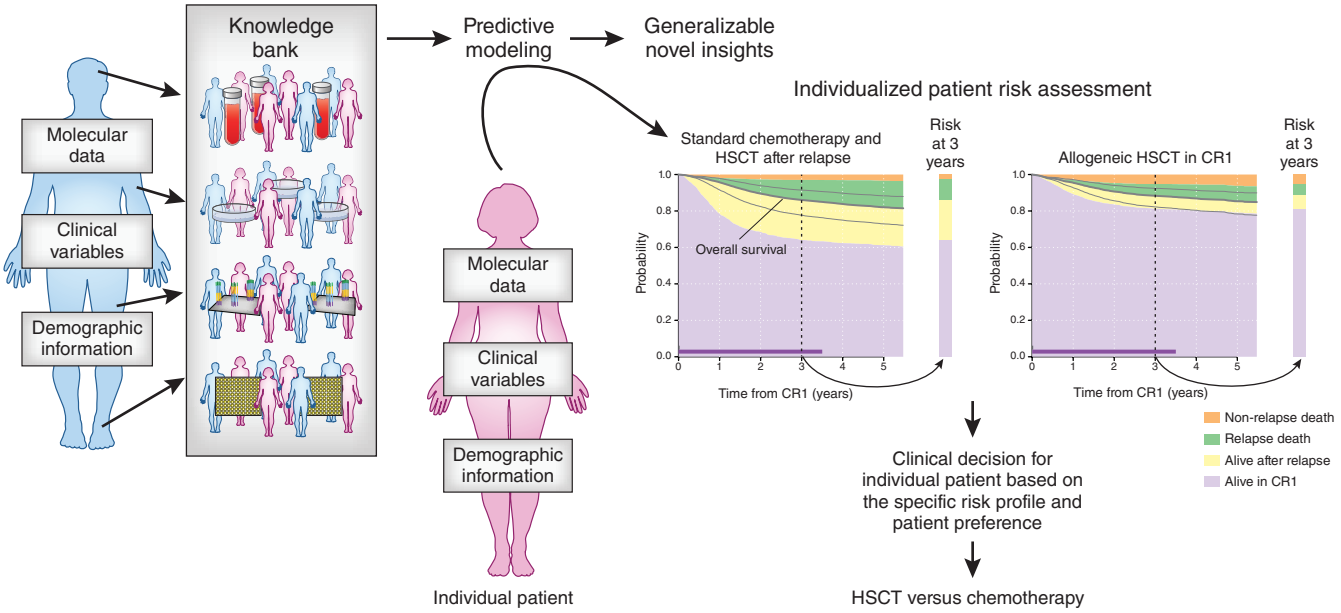

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Figure 1 The knowledge bank approach. A knowledge bank accrues information on parameters that are relevant to the disease and its treatment, permitting novel, generalizable insights about the disease and its subgroups. An individual patient's specific characteristics are reflected upon the knowledge bank to define the individual's risk profile for different treatment choices. As the number of participants in the knowledge bank grows, the confidence in predictions for individual patients continuously grows. The sediment plots show the risk of each outcome over time for each treatment choice. HSCT, hematopoietic stem cell transplantation; CR1, first complete remission.

and a randomized, appropriately controlled study is feasible to address this question and further validate the selection model before implementation. Yet, if the ultimate goal is to use knowledge banks to improve healthcare and we are faced with an ever-increasing diversity and complexity of disease, data emerging from larger knowledge banks may not be tractable to test using traditional clinical trial designs. Defining quality standards, particularly for clinical data and metrics, around what is considered to be an effective intervention and the path to broader implementation and regulatory approval will be vital if we are to effectively realize the promise of knowledge banks for clinical medicine.

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Convergence and divergence in sex-chromosome evolution

Catherine L Peichel

A sequence assembly of the chicken W chromosome enables reconstruction of the gene content of the W chromosome across 14 bird species and shows striking similarities in the maintenance of broadly expressed and dosage-sensitive genes on highly degenerate sex chromosomes in both birds and mammals. However, the chicken W chromosome is not enriched for genes with expression in female-specific tissues, providing an intriguing contrast to the acquisition and amplification of genes with testis-specific expression on mammalian Y chromosomes and suggesting that the inheritance of chromosomes solely through females or males can lead to different evolutionary outcomes.

In many eukaryotic species, males and females have the same complement of chromosomes with one very important exception: the sex chromosomes. Usually discovered when comparing the karyotypes of males and females from the same species, sex chromosomes are unique parts of the genome for which one sex has a similar, or homomorphic, chromosome pair while the other sex has a dissimilar, or heteromorphic, chromosome pair. For example, mammals possess an XX/XY sex-chromosome system in which males have a heteromorphic XY chromosome pair and females have a homomorphic XX chromosome pair. By contrast, birds have a ZZ/ZW sex-chromosome system in which males have a homomorphic ZZ pair and females have a heteromorphic ZW pair. Sex chromosomes are not confined to birds and mammals, and both XY and ZW

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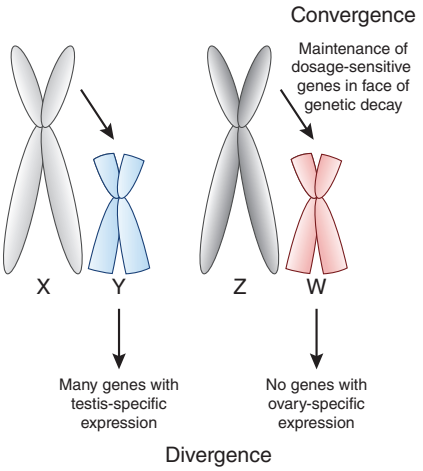

Figure 1 Schematics of the X and Y chromosomes from a human male karyotype (left) and of the Z and W chromosomes from a chicken female karyotype (right). The Y and W chromosomes have both undergone genetic decay with maintenance of dosage-sensitive genes, an example of convergence. However, they also exhibit divergence, whereby many genes on the Y chromosome are expressed in male-specific tissues, whereas the genes on the W chromosome are not restricted to expression in female-specific tissues.

sex-chromosome systems have independently and repeatedly evolved across the tree of life[1]. In this striking example of convergent evolution, suppression of recombination between the X and Y (or Z and W) chromosomes ultimately results in highly degenerate Y or W chromosomes, as is evidenced by karyotypes of the sex with the heteromorphic pair (**Fig. 1**). A new study by David Page and colleagues[2] shows that this remarkable convergence even extends to the types of genes that are maintained in the face of extensive gene loss on mammalian Y and avian W chromosomes. However, this study also hints that there is divergence in the genetic makeup of Y and W sex chromosomes, as each only evolves in the environment of one of the two sexes.

Sex-chromosome convergence

These new insights were obtained by overcoming technical challenges to sequence and assemble the chicken W chromosome. Because of the accumulation of highly repetitive sequences on degenerate sex chromosomes, these chromosomes are often excluded from genome assemblies; a standard next-generation sequencing approach is inadequate for assembly and annotation. Dedicated work by David Page and colleagues has previously generated high-quality assemblies of several mammalian Y chromosomes and demonstrated that these chromosomes have adopted two strategies to survive the ravages of degeneration[3–7]. First, gene families that are expressed in the testis and contribute to male fertility have been acquired and amplified on Y chromosomes. Second, single-copy genes that are expressed in many tissues and are predicted to be dosage sensitive are maintained under purifying selection on Y chromosomes. The current study demonstrates that purifying selection on avian W chromosomes has also maintained genes that are widely expressed and are predicted to be dosage sensitive[2]. Strikingly similar patterns have been found for the genes maintained on independently evolved Y chromosomes in both fish[8] and flies[9].

This remarkable convergence in the maintenance of dosage-sensitive genes on degenerate sex chromosomes inspires some reevaluation of the need for the evolution of dosage-compensation mechanisms. It had long been assumed that loss of genes on degenerate sex chromosomes should select for a mechanism to maintain gene-dosage balance between sex chromosomes and autosomes in the heterogametic sex. However, recent findings have suggested that dosage compensation has not arisen in many different species with degenerate sex chromosomes[10]. Taken together with the convergent maintenance of dosage-sensitive genes on both Y and W chromosomes, these findings might instead prompt us to ask why dosage-compensation mechanisms have evolved at all.

Sex-chromosome divergence

Not everything is the same on the mammalian Y and avian W chromosomes. As mentioned above, genes expressed specifically in the testis have been acquired and even amplified on mammalian Y chromosomes[3,4,6,7,11]. In contrast, only one gene family is amplified on the chicken W chromosome, and the expression of genes that are maintained on the chicken W chromosome does not seem to be restricted to female-specific tissues[2]. What might explain these differences? Importantly, Y chromosomes are only present in males and are transmitted through the male germline, whereas W chromosomes are only present in females and are transmitted through the female germline. Thus, Y and W chromosomes are evolving in very different environments. Because there is usually greater variance in mating success in males than in females, males often experience stronger sexual selection and have a lower effective population size than females. One possibility is that selection is therefore stronger to maintain male-beneficial genes on the Y chromosome than to maintain female-beneficial genes on the W chromosome[12]. However, there is also evidence that genes on bird W chromosomes do respond to female-specific selection[13]. Another possibility proposed by the authors is that the potential for competition between homologous chromosomes (that is, meiotic drive) might be higher in spermatogenesis than in oogenesis[2]. In spermatogenesis, cytoplasmic bridges connect developing sperm during and after meiosis, whereas competition between homologous chromosomes for inclusion in the egg rather than the polar body is restricted to the first meiotic division during oogenesis. Interestingly, female meiotic drive has also been proposed as a potent evolutionary force in the evolution of mammalian karyotypes[14]. Still, without further data, the reasons for the observed differences in gene content between Y and W chromosomes remain unclear.

More high-quality sequence assemblies are needed to ascertain whether XY and ZW sex-chromosome systems always differ in the maintenance of sex-specific genes. In particular, it will be important to compare XY and ZW systems in very closely related species, such as those found in many groups of fish and non-avian reptiles[15], to minimize the confounding effects of biological differences between the systems and gain further insights into the unique evolutionary dynamics of sex chromosomes.

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