Am. J. Hum. Genet. 64:24–30, 1999

MOLECULAR EVOLUTION '99
Concerted Evolution: Molecular Mechanism and Biological Implications

Daiqing Liao

Department of Microbiology and Infectious Diseases, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, Quebec

A surprisingly large fraction of the eukaryotic genome is repetitive. More than one third of the human genome consists of interspersed repetitive DNA, and tandemly repeated DNA sequences may occupy as much as 10% of the human genome. The majority of the repetitive sequences are nongenic; the rest encode multigene families. The genomic organization of repetitive DNA sequences takes different forms: these repetitive sequences either disperse throughout the genome, as with short interspersed sequences (SINEs), long interspersed sequences (LINEs), and transposable elements, or, like tRNA genes and human histone genes, they may cluster in one or a few chromosomal regions. Multigene families, including those for ribosomal RNAs (rRNAs) and small nuclear RNAs (snRNAs) (Pavelitz et al. 1995), as well as noncoding sequences such as satellite DNA, minisatellite sequences, and microsatellite sequences (Charlesworth et al. 1994), are often arranged in tandem arrays. Despite the abundance of repetitive DNA in the genomes of eukaryotic organisms, the biological functions, if any, of noncoding repetitive sequences remain elusive. However, most repetitive sequences, whether coding or noncoding, exhibit an unexpected property: they evolve in a concerted fashion.

What Is Concerted Evolution?

When members of a repetitive family are compared, greater sequence similarity is found within a species than between species, suggesting that members within a repetitive family do not evolve independently of each other. The molecular process that leads to homogenization of DNA sequences belonging to a given repetitive family is called "concerted evolution" (reviewed in Elder and Turner 1995). Concerted evolution is a universal biological phenomenon. In species ranging from bacteria to mammals, most repetitive-gene families thus far examined undergo concerted evolution. In *Escherichia coli,* there are seven operons encoding rRNAs 16S, 23S, and 5S. For each of these genes, rDNA sequences that are represented in fully processed rRNA are essentially identical among all of the seven operons (Blattner et al. 1997). For example, the sequence divergence of all seven 16S rRNA genes is only 0.195% in *E. coli* strain K-12, whereas, in a closely related bacterial species, *Haemophilus influenzae,* the coding regions of six ribosomal operons are entirely identical (Fleischmann et al. 1995); however, between *E. coli* K-12 and *H. influenzae* RD, the sequence divergence of the 16S rRNA gene is 5.90%.

In most eukaryotic organisms, the ribosomal genes are tandemly arrayed and undergo concerted evolution (Arnheim et al. 1980; Coen et al. 1982; Schlötterer and Tautz 1994). Concerted evolution is also very well documented in the primate *RNU2* locus, which encodes the U2 snRNA. It has been shown that the U2 tandem array, established early in the primate lineage, has been stable for >35 million years and has evolved in a concerted fashion in various primate lineages (Pavelitz et al. 1995). Specifically, Old World monkeys (baboons, macaques, and talapoins) have an 11-kb U2 repeat unit, whereas apes (gibbons, orangutans, gorillas, and chimpanzees) and humans have a 6-kb repeat unit (Matera et al. 1990). Subsequently, it had been shown that the 5-kb difference between Old World monkeys and the hominoid U2 repeat unit is due to homologous excision of a 5-kb sequence of a 6-kb provirus, which left behind a 1-kb-long solo long terminal repeat (LTR) (Pavelitz et al. 1995). Thus, concerted evolution spread deletions of >5 kb, from one repeat to all other copies in the ancestral hominoid genome. Concerted evolution has also been observed in protein-coding multigene families, such as those encoding histones (Coen et al. 1982) and ubiquitin (Nenoi et al. 1998), as well as in noncoding sequences ranging from vast α satellites to dispersed simple repeats (Elder and Turner 1995).

Both the general phenomenon of concerted evolution and the underlying mechanisms have been reviewed elsewhere (Dover et al. 1993; Jinks-Robertson and Petes 1993; Elder and Tuner, 1995). More-recent studies, discussed here, provide fresh insights into molecular mech-

Received September 12, 1998; accepted for publication November 13, 1998; electronically published December 22, 1998.

Address for correspondence and reprints: Dr. Daiqing Liao, Department of Microbiology and Infectious Diseases, Université de Sherbrooke, 3001 12e Avenue Nord, Sherbrooke, Quebec, Canada J1H 5N4. E-mail: dliao@courrier.usherb.ca

© 1999 by The American Society of Human Genetics. All rights reserved.

0002-9297/99/6401-0006$02.00

anisms of concerted evolution, as well as into its profound biological implications.

How Many Routes to Concerted Evolution?

Greater sequence similarity of a repetitive multigene family within a species than between species implies that organisms possess mechanisms that maintain sequence homogeneity in a repetitive-gene family. The intraspecific homogenization of repetitive-sequence arrays is believed to be the result of a number of DNA recombination, repair, and replication mechanisms, such as unequal crossing-over between repeating units, gene conversion, and gene amplification (Liao et al. 1997, and references therein).

Recent studies on multigene families encoding snRNA U2 and rRNA have provided some new insights into the mechanism of concerted evolution. The human *RNU2* locus consists of multiple tandemly arrayed 6.1-kb repeats (see fig. 1*A*) and resides in a single chromosomal region at 17q21-22, just telomeric to the human *BRCA1* locus. The copy number of the 6.1-kb U2 repeat varies widely within individuals and populations, ranging from 5 to >30 copies per U2 tandem array, suggesting a high level of ongoing recombination within or between *RNU2* loci (Liao et al. 1997). Analysis of several polymorphic markers has indicated that individual U2 tandem arrays are entirely homogeneous for specific polymorphic alleles, although different alleles of each markers can occur in any combination. Thus, sequence homogenization occurs primarily along chromosomal lineages. Studies of sequences flanking the U2 tandem array have revealed tight association of specific haplotypes in left and right junctions of the U2 array. Therefore, individual U2 arrays do not exchange flanking markers, despite independent assortment and subsequent homogenization of specific polymorphic markers within a U2 array. In view of these results, it has been proposed that the primary driving force for concerted evolution of tandemly repeated multigene families is intrachromosomal homogenization; interchromosomal genetic exchange is much rarer and proceeds by gene conversion–like mechanisms (fig. 1*B;* also see Liao et al. 1997).

In studying polymorphisms within the internal transcribed spacer of rDNA arrays in populations of *Drosophila melanogaster,* Schlötterer and Tautz (1994) and, more recently, Dover and colleagues (Polanco et al. 1998), found that individual rDNA arrays are homogenized for different polymorphic alleles, indicating that intrachromosomal recombination events occur at rates much higher than those for recombination between homologous chromosomes at the rDNA loci. Similarly, in the plant *Arabidopsis thaliana,* two arrays encoding

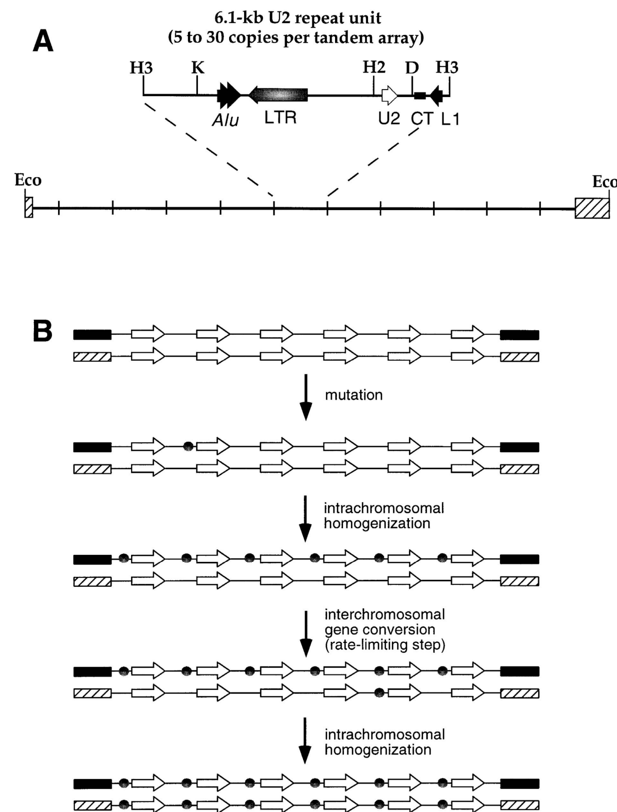

Figure 1 Model for the molecular mechanism of concerted evolution. *A,* Organization of tandemly arrayed human U2 snRNA genes (the *RNU2* locus). The copy number of the 6.1-kb U2 repeat per tandem array varies widely in humans, ranging from 5 to >30. The structure of the U2 repeat unit is depicted in an enlarged form at the top (Pavelitz et al. 1995). Some sequence elements within the U2 repeat are indicated, including two tandemly repeated *Alu* sequences, an LTR, a CT microsatellite, and a truncated L1 element. The U2 snRNA coding region is shown as an unblackened arrow. Restriction sites are as follows: D = *Dra*I; Eco = *Eco*RI; H2 = *Hinc*II; H3 = *Hind*III; K = *Kpn*I. *B,* Model for concerted evolution of tandemly repeated multigene families. Two tandem arrays, together with their flanking DNA, are illustrated. The coding sequences are depicted as unblackened arrows, and the intergenic spacers are depicted as lines. The flanking sequences of the two arrays are differently labeled (as either blackened or cross-hatched boxes). A mutation arises in a repeat unit on the top array (indicated by a black circle), which is spread rapidly throughout the top array by intrachromosomal homogenization mechanisms. This mutation is then spread farther, to the lower tandem array, by interchromosomal gene conversion. Note that no exchange of flanking sequences is involved in such interallelic events. Finally, the mutation is fixed in the second array, by additional rounds of intrachromosomal homogenization (see Liao et al. 1997).

~1,500 rRNA genes occur on different chromosomes, with specific polymorphic alleles largely homogeneous in each rDNA array. Interestingly, different polymorphic alleles can be found within an individual array, but specific alleles exist in homogeneous adjacent units, not dispersed throughout an rDNA array (Copenhaver and Pi-

kaard 1996). Moreover, in the mouse germ line, gene conversion between duplicated genes on the same chromosome occurs at a frequency higher than that which occurs when they reside on different chromosome (Murti et al. 1992, 1994). These observations are fully consistent with the proposal that intrachromosomal homogenization is faster than interchromosomal recombination, as described above.

Specific mechanisms responsible for intrachromosomal homogenization are unknown, but either intrachromosomal gene conversion or unequal sister-chromatid exchange (USCE) could, in principle, account for intrachromosomal recombination in concerted evolution. Both USCE and gene conversion can explain the observed variation in copy number from 5 to >30 U2 repeats per U2 array, since gene conversion can also lead to expansion or contraction of tandemly arrayed genes (Liao et al. 1997, and references therein).

Gene Conversion in Concerted Evolution

To account for sequence homogeneity of a repetitive multigene family within a population or a species, there must be genetic exchange between homologous or nonhomologous chromosomes. Because of the absence of reciprocal exchange in markers flanking the U2 tandem array, the most probable mechanism for interchromosomal genetic exchange is gene conversion (Liao et al. 1997). Gene conversion (see Schimenti 1999 [in this issue]) is the nonreciprocal transfer of genetic information between similar sequences, in which exchange of flanking DNA is not involved. Gene conversion is very precise, leading to homogenization of only specific DNA regions, such as coding sequences; little flanking-sequence identity is required (Abdulkarim and Hughes 1996) for efficient gene conversion. The frequency of interchromosomal gene conversion need not be high, since theoretical modeling has predicted that very low levels of gene conversion, between both homologues and nonhomologues, are effective in the homogenization of multigene families (Ohta and Dover 1983). It has been shown that gene conversion is responsible for homogenization of dispersed genes in bacteria (Abdulkarim and Hughes 1996) and yeast (Amstutz et al. 1985). Thus, it is reasonable to assume that gene conversion is the general mechanism responsible for concerted evolution of all dispersed genes (see Murti et al. 1994). Especially rapid gene conversion is believed to be responsible for concerted evolution of rDNA gene arrays in the lizard *Heteronotia binoei* (Hillis et al. 1991).

Cis- and Trans-Factors That Influence Concerted Evolution

It appears intuitively true that, because members of a tandemly repeated–gene family reside in close proximity, this organization should allow for efficient homogenization. Indeed, in higher eukaryotes, gene conversion seems to occur mainly between genes that are close to each other, although sometimes they may be in head-to-head orientation rather than arrayed tandemly (Benedict et al. 1996). Simulation studies also have indicated that effective homogenization of dispersed genes by gene conversion can only be achieved when the number of dispersed genes is small (Ohta and Dover 1983). This view is consistent with the observation that intrachromosomal homogenization is much faster than interchromosomal exchange. Homogenization of widely interspersed genes has been demonstrated only in bacteria and yeast, organisms whose genomic complexity is relatively small.

The enzymology involved in sequence homogenization is not known. Many proteins in DNA recombination, replication, and repair are likely to play roles in various steps of homogenization. Some clues may come from the study of sequence homogenization of the *tuf* genes of *Salmonella typhimurium*. Abdulkarim and Hughes have shown that general recombination enzymes RecA, -B, -C, and -D are required for gene conversion, whereas, surprisingly, mismatch-repair enzymes MutS, -H, -L, and -U interfere with the homogenization process. Strains lacking functional RecA and RecB essentially abolish gene conversion, whereas mutations inactivating MutS and MutL increase the rate of homogenization by three orders of magnitude (Abdulkarim and Hughes 1996). The results of studies in human cells appear to be consistent with these observations. Despite the microsatellite instability that is the hallmark of human mismatch-repair defects, U2 tandem arrays in human cells lacking mismatch-repair or nucleotide excision–repair genes are as homogeneous as are those in cells with normal repair functions (C. Jiang and D. Liao, unpublished data).

Population Behaviors of Multigene Families

It is important to recognize that concerted evolution is a complex process. It involves homogenization of a mutation in an array in a genome containing both homologous and nonhomologous chromosomes. Thus, to understand the concerted evolution of multigene families, the population dynamics of these chromosome lineages must be investigated. Owing to its relative small size, uniform structure, and single chromosomal location, the human *RNU2* locus provides an excellent system with which to study the population behaviors of multigene families. Initial analysis of U2 genes in diverse

human populations ranging from African Pygmies to Indian tribes in South America has yielded insights into the molecular mechanism of concerted evolution and also into human genome diversity and population history (Liao et al. 1997). First, alleles of polymorphic markers within the U2 tandem arrays are present in all populations studied, suggesting that they have persisted for most of human history. Thus, elimination or fixation of a particular allele within a multigene family in a population by concerted evolution may take an exceedingly long time. Second, at least five types of different U2 tandem arrays have been identified thus far, all of which are present in African populations. Consistent with a growing body of genetic data suggesting that modern non-African populations resulted from a recent migration from Africa, only two of these five variants are represented in diverse non-African populations. Third, the two types of *RNU2* loci in non-African populations exist in linkage disequilibrium with flanking markers, suggesting that only a limited number of people migrated out of Africa and that their descendants populated the rest of the world. Moreover, linkage disequilibrium of *RNU2* loci in diverse non-African populations also implies that any interchromosomal genetic-exchange event at the *RNU2* locus is very rare, and thus it might represent the rate-limiting step in concerted evolution (fig. 1*B;* also see Liao et al. 1997).

A species-specific mutation must arise initially in one repeat in a particular array in a single individual; the dynamics of its spread will depend on rates of recombination within and between chromosomes and will be subject to both natural selection and random genetic drift. Early computer simulations indicated that, if the mutation rate is high relative to the rate of spread of a variant through an array, heterogeneity is expected among the repeating units; only if mutation is slow relative to fixation would homogeneous arrays result (reviewed in Elder and Turner 1995). Because most mutations are believed to be selectively neutral, and because fixation of a neutral allele is inefficient in large populations, genetic drift is often inadequate to explain the concerted evolution of a group of genes.

The rate at which active monitoring and gene homogenization must occur may depend on the biological system concerned. The rate of sequence homogenization of the two *Salmonella tuf* genes by gene conversion is ~1,000-fold higher than that of spontaneous mutation. Because of this high homogenization rate, the DNA sequence of the two *tuf* genes is 99% identical. The rate of recombination at the bacterial rRNA operons may be even higher, as much as 1,000-fold higher than that of gene conversion at the *Salmonella tuf* loci (Lan and Reeves 1998). Indeed, there are many more rRNA genes to be homogenized, so this additional level of activity may be needed for effective homogenization. These observations support the view that concerted evolution of multigene families may not be simply a result of stochastic recombination but, rather, may reflect a requirement for the cell to maintain sequence homogeneity within a multigene family.

How Do Multigene Families Escape from Concerted Evolution?

The mechanism of concerted evolution described above is based on studies with multigene families. Whether this model applies to repetitive noncoding DNA is unknown, although theoretical considerations and some sequence data appear to indicate that concerted evolution of repetitive noncoding DNA sequences may, by and large, proceed through similar mechanisms (Elder and Turner 1995). However, it is important to bear in mind that, although some repetitive noncoding sequences exhibit apparent species-specific sequence homogeneity, much of this may reflect recent amplification and transposition, rather than active sequence homogenization. These alternatives can be distinguished by the pattern of divergence among orthologous sequences in several closely related species. Phylogenetic analysis of repetitive sequences should consistently reveal cohesive grouping of sequences within a species if they undergo concerted evolution. Conversely, if there is no sequence homogenization among members of a repetitive family, one would not necessarily expect that they form a species-specific monophyletic cluster; some more-divergent members may be scattered within the phylogenetic tree, and they may even group together with sequences from different species. One excellent example in this regard is the analysis of multigene families of the vertebrate immune system. These multigene families were initially thought to undergo concerted evolution, but recent analyses by Nei et al. (1997) have shown that multigene families of the immune system do not evolve in a concerted fashion; rather, they evolve by the so-called birth-and-death process (Nei et al. 1997). First, these workers found that members of the major histocompatibility complex (MHC) and immunoglobulin (Ig) gene families from the same species are not always more closely related to one another than to the genes from different species, and no significant genetic exchange among the members of these multigene families was discernible. Second, duplications of MHC and Ig genes are common, and their pseudogenes are abundant. Thus, in the birth-and-death model of evolution, duplicate genes are produced in a gene family; some members of the family diverge functionally, others become pseudogenes because of deleterious mutations, whereas still others are deleted outright from the genome. As a result, a birth-and-death model for gene evolution would predict the coexistence of divergent groups of genes with highly ho-

mologous genes plus a substantial number of pseudogenes in a multigene family.

DNA sequence duplication is believed to be the main source of new genes in evolution. Duplicated genes may diverge and acquire new functions, or they may become functionally inactivated and remain in the genome as pseudogenes. The third alternative is that all copies may be maintained in their original form; the homogenizing effect of concerted evolution favors this last possibility and acts to slow genetic and, hence, functional diversity. Clearly, the emergence of genetic novelty shows that this process is not universal. It is now clear that not all repetitive DNA families undergo concerted evolution, as discussed above for the MHC and Ig multigene families (Nei et al. 1997). In addition, some *Alu* elements (Koop et al. 1986) and some *LTR* elements (Liao et al. 1998) seem to be free to diverge from one another. Furthermore, the rate of homogenization of a gene family does not appear to be uniform throughout its evolutionary history. Sequence analyses of globin genes (see Goodman 1999 [in this issue]) in various species indicate that some duplicated genes may initially undergo homogenization by gene conversion but that, once the sequences have diverged sufficiently, this mechanism is no longer efficient and that genes therefore evolve independently (Brunner et al. 1986; Murti et al. 1992).

The chromosomal locations of duplicated genes may also affect whether they undergo active recombination, as required for concerted evolution (Murti et al. 1994). It is known that recombination is suppressed in some chromosomal regions, such as centromeres and telomeres (Charlesworth et al. 1994). Cis-acting elements may also influence whether duplicated genes undergo concerted or divergent evolution. One example can be found in the early chorionic-gene families of the silk moth *Boxbyx mori.* There are two families of early chorionic genes, *ErA* and *ErB,* closely linked on one chromosome. The genes of the *ErA* family exhibit 96% sequence identity, whereas those in the *ErB* family exhibit only 63% sequence identity. Sequence analysis has suggested that microsatellite-like simple repeats present in the *ErA* family but not in the *ErB* family may account for the difference in homogenization, because simple sequence repeats can be the site for initiation of gene conversion (Hibner et al. 1991). Microsatellite sequences in the human *RNU2* locus may also play a role in concerted evolution (Liao and Weiner 1995).

Exploiting Concerted Evolution for Novel Biological Purposes

It is interesting to note that multigene families undergoing concerted evolution generally encode abundant RNA or protein molecules, such as rRNAs, snRNAs, and histones. For example, there are as many as 10 million copies of rRNA per cell, and, because rRNAs are structural molecules, translation is not available, as it would be for a protein-coding RNA, to amplify expression of a primary gene product. Thus, transcription of a single ribosomal gene would clearly not suffice; multiple gene copies are necessary to meet the demand for ribosomal subunits in a growing cell. However, because these abundant molecules function only when they are assembled into large complexes, homogeneity of rRNAs is crucial if all of the steps of ribosome assembly and translation are to proceed normally. One can therefore envision that a possible biological function of concerted evolution is to maintain homogeneous gene copies in a family so that homogeneous transcripts can be produced. Thus, concerted evolution can be viewed as one form of "quality control" in the production of components for complex macromolecular machines in the cell.

Support for this view comes from study of the rDNA genes in flatworm species *Dugesia mediterranea,* in which quality control is managed differently. In this species, 18S rRNA genes are, in fact, heterogeneous, but only one type of 18S rRNA gene appears to be expressed (Carranza et al. 1996). Presumably, the simultaneous expression of heterogeneous rRNA genes would be deleterious to cells in the flatworm.

Paradoxically, concerted evolution could also lead to biological diversity and population differentiation. It has been hypothesized that genes evolving by concerted evolution generate selective pressure on the gene of their cognate interacting protein (Dover 1993). The observed species-specific transcription of rRNA genes by RNA polymerase I (Pol I) may lend support to this view. Unlike class II– and class III–specific transcription factors (TATA box binding protein [TBP] and TBP-associated factors [TAFs]), Pol I transcription-initiation factor (TIF-IB/SL1) exhibits pronounced species specificity. It is thought that concerted evolution randomly samples and homogenizes species-specific mutations of the rDNA arrays including the Pol I promoter region, whereby such concerted change of promoter sequences would drive adaptive evolution (coevolution) of species-specific transcription factors (Heix and Grummt 1995). Although the biological significance of species-specific Pol I transcription remains unclear, it might, conceivably, contribute to species differentiation. Indeed, concerted evolution may be a profound genetic force promoting speciation. It is well known that proteins involved in gamete recognition undergo rapid, adaptive evolution and that gamete interactions during fertilization exhibit species specificity. It remains unclear what evolutionary force creates this specificity in internally fertilized species such as mammals. Recent experimental results have suggested that concerted evolution of the egg receptor for sperm protein may be the molecular basis that gives rise

to species-specific fertilization (Swanson and Vacquier 1998).

Summary

Concerted evolution is a fundamental process. It operates in all organisms. The molecular mechanism underlying concerted evolution has just begun to emerge. Genetic analyses of multigene families such as rDNA and snRNA genes in diverse populations will continue to yield useful information regarding the population dynamics of multigenes and will provide clues to the mechanism of concerted evolution. The challenge ahead is to establish an experimental system to investigate the molecular details of sequence homogenization during concerted evolution, particularly in higher eukaryotes.

Acknowledgments

My research on concerted evolution started in the laboratory of Dr. Alan Weiner. I thank him for continuous encouragement, insightful discussion, and critical reading of the manuscript. I am also grateful to Dr. John Ashkenas for thoughtful suggestions and editorial assistance. I am a Chercheur-Boursier Junior I of the Fonds de la Recherche en Santé du Québec. This work was supported by Medical Research Council of Canada grant MT-14109.

References

Abdulkarim F, Hughes D (1996) Homologous recombination between the *tuf* genes *of Salmonella typhimurium.* J Mol Biol 260:506–522

Amstutz H, Munz P, Heyer WD, Leupoid U, Kohli J (1985) Concerted evolution of tRNA genes: intergenic conversion among three unlinked serine tRNA genes in *S. pombe.* Cell 40:879–886

Arnheim N, Krystal M, Schmickel R, Wilson G, Ryder O, Zimmer E (1980) Molecular evidence for genetic exchanges among ribosomal genes on nonhomologous chromosomes in man and apes. Proc Natl Acad Sci USA 77:7323–7327

Benedict MQ, Levine BJ, Ke ZX, Cockburn AF, Seawright JA (1996) Precise limitation of concerted evolution to ORFs in mosquito Hsp82 genes. Insect Mol Biol 5:73–79

Blattner FR, Plunkett G III, Bloch CA, Perna NT, Burland V, Riley M, Collado-Vides J, et al (1997) The complete genome sequence of *Escherichia coli* K-12. Science 277:1453–1474

Brunner AM, Schimenti JC, Duncan CH (1986) Dual evolutionary modes in the bovine globin locus. Biochemistry 25: 5028–5035

Carranza S, Giribet G, Ribera C Baguna, Riutort M (1996) Evidence that two types of 18S rDNA coexist in the genome of *Dugesia* (*Schmidtea*) *mediterranea* (*Platyhelminthes, Turbellaria, Tricladida*). Mol Biol Evol 13:824–832

Charlesworth B, Sniegowski P, Stephan W (1994) The evolutionary dynamics of repetitive DNA in eukaryotes. Nature 371:215–220

Coen E, Strachan T, Dover G (1982) Dynamics of concerted evolution of ribosomal DNA and histone gene families in the *melanogaster* species subgroup of *Drosophila.* J Mol Biol 158:17–35

Copenhaver GP, Pikaard CS (1996) Two-dimensional RFLP analyses reveal megabase-sized clusters of rRNA gene variants in *Arabidopsis thaliana* suggesting local spreading of variants as the mode for gene homogenization during concerted evolution. Plant J 9:273–282

Dover GA (1993) Evolution of genetic redundancy for advanced players. Curr Opin Genet Dev 3:902–910

Dover GA, Linares AR, Bowen T, Hancock JM (1993) Detection and quantification of concerted evolution and molecular drive. Methods Enzymol 224:525–541

Elder JF Jr, Turner BJ (1995) Concerted evolution of repetitive DNA sequences in eukaryotes. Q Rev Biol 70:297–320

Fleischmann RD, Adams MD, White O, Clayton RA, Kirkness EF, Kerlavage AR, Bult CJ, et al (1995) Whole-genome random sequencing and assembly of *Haemophilus influenzae.* Science 269:496–512

Goodman M (1999) The genomic record of humankind's evolutionary roots. Am J Hum Genet 64:31–39 (in this issue)

Heix J, Grummt I (1995) Species specificity of transcription by RNA polymerase I. Curr Opin Genet Dev 5:652–656

Hibner BL, Burke WD, Eickbush TH (1991) Sequence identity in an early chorion multigene family is the result of localized gene conversion. Genetics 128:595–606

Hillis DM, Moritz C, Porter CA, Baker RJ (1991) Evidence for biased gene conversion in concerted evolution of ribosomal DNA. Science 251:308–310

Jinks-Robertson S, Petes TD (1993) Experimental determination of rates of concerted evolution. Methods Enzymol 224:631–646

Koop BF, Miyamoto MM, Embury JE, Goodman M, Czelusniak J, Slightom JL (1986) Nucleotide sequence and evolution of the orangutan epsilon globin gene region and surrounding Alu repeats. J Mol Evol 24:94–102

Lan R, Reeves PR (1998) Recombination between rRNA operons created most of the ribotype variation observed in the seventh pandemic clone of *Vibrio cholerae.* Microbiology 144:1213–1221

Liao D, Pavelitz T, Kidd JR, Kidd KK, Weiner AM (1997) Concerted evolution of the tandemly repeated genes encoding human U2 snRNA (the *RNU2* locus) involves rapid intrachromosomal homogenization and rare interchromosomal gene conversion. EMBO J 16:588–598

Liao D, Pavelitz T, Weiner AM (1998) Characterization of a novel class of interspersed LTR elements in primate genomes: structure, genomic distribution, and evolution. J Mol Evol 46:649–660

Liao D, Weiner AM (1995) Concerted evolution of the tandemly repeated genes encoding primate U2 small nuclear RNA (the RNU2 locus) does not prevent rapid diversification of the (CT)n.(GA)n microsatellite embedded within the U2 repeat unit. Genomics 30:583–593

Matera AG, Weiner AM, Schmid CW (1990) Structure and evolution of the U2 small nuclear RNA multigene family in primates: gene amplification under natural selection? Mol Cell Biol 10:5876–5882

Murti JR, Bumbulis M, Schimenti JC (1992) High-frequency

germ line gene conversion in transgenic mice. Mol Cell Biol 12:2545–2552

——— (1994) Gene conversion between unlinked sequences in the germline of mice. Genetics 137:837–843

Nei M, Gu X, Sitnikova T (1997) Evolution by the birth-and-death process in multigene families of the vertebrate immune system. Proc Natl Acad Sci USA 94:7799–7806

Nenoi M, Mita K, Ichimura S, Kawano A (1998) Higher frequency of concerted evolutionary events in rodents than in man at the polyubiquitin gene VNTR locus. Genetics 148: 867–876

Ohta T, Dover GA (1983) Population genetics of multigene families that are dispersed into two or more chromosomes. Proc Natl Acad Sci USA 80:4079–4083

Pavelitz T, Rusche L, Matera AG, Scharf JM, Weiner AM (1995) Concerted evolution of the tandem array encoding primate U2 snRNA occurs in situ, without changing the cytological context of the *RNU2* locus. EMBO J 14: 169–177

Polanco C, Gonzalez AI, de la Fuente A, Dover GA (1998) Multigene family of ribosomal DNA in *Drosophila melanogaster* reveals contrasting patterns of homogenization for IGS and ITS spacer regions: a possible mechanism to resolve this paradox. Genetics 149:243–256

Schimenti JC (1999) Mice and the role of unequal recombination in gene-family evolution. Am J Hum Genet 64:40–45 (in this issue)

Schlötterer C, Tautz D (1994) Chromosomal homogeneity of *Drosophila* ribosomal DNA arrays suggests intrachromosomal exchanges drive concerted evolution. Curr Biol 4: 777–783

Swanson WJ, Vacquier VD (1998) Concerted evolution in an egg receptor for a rapidly evolving abalone sperm protein. Science 281:710–712