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Genome Plasticity and Chromosome Evolution

All life as we know it traces back to a single common ancestor. The diversity of living organisms could not have been achieved in the 3–4 billion years they have existed on earth without a high level of genome plasticity. Here we will explore some of the aspects of this plasticity that are most relevant to understanding the behavior of human chromosomes. The common origin of all life forms was strongly supported by Charles Darwin, whose theory of evolution by natural selection provided a powerful explanation for the enormous diversity of living organisms. Genetics and molecular biology have confirmed this unity, demonstrating that all organisms store their genetic information in DNA or RNA and use a virtually universal genetic code for translating this information into protein sequences. Genes, too, show a remarkable degree of conservatism. As an example, over 70 human genes are already known that can function in yeast, substituting for the correspond-

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ing defective yeast gene (National Center for Biotechnology Information, http://www.ncbi.nim.nih.gov/Bassett/cerevisiae/index.htmi). A recent study in *Drosophila* used saturation mutagenesis of a 67-kb region to identify 12 new expressed genes. Nearly all these genes had close relatives in the human and round worm (*Caenorhabditis elegans*) databases. Half were present in the yeast (*Saccharomyces cerevisiae*) database, and a few were even present in the bacterial databases (Maleszka et al., 1998). This level of sequence conservation is remarkable, especially since warm-blooded birds and mammals have evolved a rather different genome organization, marked by increased heterogeneity in base composition, with highly GC-rich and GC-poor isochores and attendant changes in codon usage (Bernardi, 1995; see also Chapter 7).

Sequencing the genome of the round worm, *C. elegans*, is essentially complete, with only minor gaps (The *C. elegans* Sequencing Consortium, 1998). The 97 million–bp genome contains more than 19,000 genes, with considerably more sequence similarity of the inferred proteins to human proteins than to those of yeast or bacteria. Analyses of amino acid sequences of proteins and nucleotide sequences of DNA are now widely used to clarify the phylogenetic relationships between different species and larger taxonomic groups. Ribosomal RNA gene sequence comparisons favor a complex, partially parasitic origin of eukaryotes (including humans) from eubacteria, archebacteria, and an unknown third source. Comparisons of the complete genomic sequences of 12 bacterial species and several yeast (eukaryotic) species has confirmed this and pointed out probable features of this third type of ancestor. Since neither eubacterian nor archebacteria have gene sequences resembling the cytoskeletal protein genes of eukaryotes, it is likely that the third life form from which eukaryotes also arose already had a cytoskeleton (Doolittle, 1998).

Genome Plasticity

The evolution of eukaryotes, and particularly multicellular metazoans, from simpler life forms has involved marked increases in genome size through processes that include gene duplication, transposition, insertion, exon shuffling, and genomic rearrangement. Gene duplication leads to an additional copy of a gene, usually as a direct tandem repeat. Unequal crossing over can lead to a third copy, and so on. For example, the *CYP2D6* gene exists as 1–13 tandem copies in different ethnic groups (Lundquist et al., 1999). Subsequent mutation may inactivate one or more of the copies or may lead to slightly altered function, so

that a multigene family is created. Surprisingly, about half of all gene duplications appear to lead to functional divergence rather than inactivation of the extra copy (Nadeau and Sankoff, 1997). Both outcomes are possible within a single duplicated gene cluster. For example, the interferon (*IFN*) gene family at 9p21–p22 consists of 15 functional genes and 11 nonfunctional pseudogenes (Strissel et al., 1998). Gene amplification may also contribute to evolution, producing multiple copies of a gene that may remain at the same locus or be widely distributed throughout the genome. Thus, the keratinocyte growth factor multigene family emerged suddenly about 5–8 million years ago in the lineage that produced humans, chimpanzees, and gorillas. It arose by 16-fold amplification of part of a 3-exon gene containing exons 2 and 3 (Kelley et al., 1992).

Genome organization fosters rapid evolution in several ways. One is the behavior of introns. Most genes are made up of multiple short coding sequences (exons), averaging 120 bp long, separated by longer, noncoding sequences (introns). Gilbert has long maintained that exons can shuffle from one gene to another as a result of a chromosomal mechanism, ectopic recombination between introns, and that this has permitted the rapid evolution of eukaryotes. Another mechanism of potentially major importance involves L1 LINE (LINE1) elements. These retrotranspose at rather high frequency (they carry their own reverse transcriptase, which favors this), and can insert into an intron of a gene, carrying with them whatever sequence is at their 3′ flank. This enables them to mobilize non-L1 sequences, including exons, and add them to an existing gene, where they will function as an additional exon (Moran et al., 1999). Each exon is usually, but not always, a functional domain, and exon shuffling can lead to the production of a protein with additional functional domains (e.g., DNA binding, kinase activity, hormone binding). Gilbert's group has estimated that all proteins that now exist on earth arose from no more than 7000, and possibly as few as 1000, exons, with exon shuffling greatly speeding up the evolution of proteins with new functions (Dorit et al., 1990). Many proteins, especially those in multigene families, are multifunctional, possibly as a result of exon shuffling. For example, the roles the imprinted *IGF2* (insulin-like growth factor 2) gene product plays in glycoprotein transport, growth and development, and tumor suppression involve three different functional domains (Desouza et al., 1997).

The presence of repeated sequences, especially those only a short distance from one another on a chromosome, greatly increases the risk of illegitimate ectopic pairing and recombination between sequences that are almost identical, that is, homologous recombination between nonsyntenic regions (Fig. 14.2). Such unequal crossing over can disrupt a functional gene; create a new gene; or

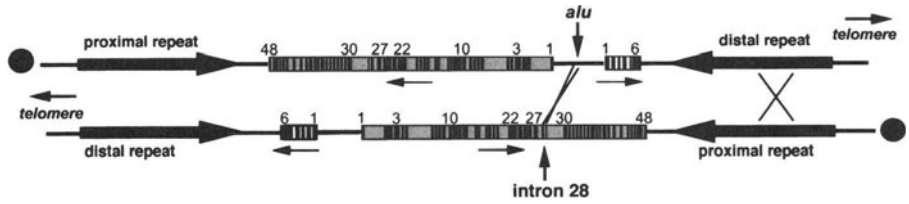

Figure 30.1. Rearrangement involving mispaired inverted repeats. Some of the exons (black) of the large *FLN1* gene and the small *emerin* gene are numbered for orientation. Arrows indicate direction of transcription. Black circles: centromeres. The inversion was mediated by unequal (ectopic) recombination between one *Alu* element between the two genes and one within intron 28 of *FLN1* (Small et al., Nat Genet 16:97, 1997).

lead to deletion, duplication, or rearrangement, as described in earlier chapters. It is worth emphasizing that the presence of inverted repeats can lead to inversion polymorphisms. Emerin is a lamin-associated nuclear membrane protein that is defective in the Emery-Dreifuss type of muscular dystrophy. The 48-kb region containing the *filamin* and *emerin* genes in Xq28 is flanked by 11-kb inverted repeats that recombine so often that the two repeats are virtually identical and the *filamin/emerin* region is in an inverted state in 33% of normal females (Fig. 30.1). Naturally, this affects recombination frequencies and the linkage map. How many such polymorphisms remain to be discovered throughout the human genome?

Repeated sequences are found in all eukaryotes. Mechanisms for reducing the frequency of illegitimate crossing over between them developed, perhaps hundreds of millions of years ago. The *MSH3* gene reduces microsatellite instability by detecting DNA mismatches in organisms as diverse as humans and yeast. Cells lacking a functional *MSH3* gene show microsatellite instability and hypermutability of a test gene, the *DHFR* locus. Two other genes involved in mismatch repair are *MSH2* and *MSH6*. The heterodimer complexes MSH2–MSH3 and MSH2–MSH6 detect mismatches. Introduction of a normal chromosome 5 (carrying the *MSH3* gene) into a uterine endometrial cancer cell line with defective *MSH3* and *MSH6* genes partially restores microsatellite stability (Drummond et al., 1997). A mechanism has also evolved for silencing (blocking) the transcription of long interspersed elements (LINEs) and short interspersed elements (SINEs): DNA methylation. The methylated DNA binds a specific protein, MCP2, which targets histone deacetylase to the DNA and converts it to hete-

rochromatin, which is not transcribed (Chapter 5). This blocks the mobility of retrotransposons. In many cancers, there is widespread hypomethylation of DNA, and this is associated with greater movement of transposable elements (Yoder et al., 1997). Some interspecific hybrids show genome-wide undermethylation of DNA and associated activation of retrotransposons and chromosome remodeling; this could play a role in karyotypic evolution (O'Neill et al., 1998).

Evolution of the Autosomes

High-resolution chromosome banding and special FISH chromosome painting techniques have shown that very few chromosome rearrangements have occurred since the divergence of humans and great apes from a common ancestor some 5–8 million years ago. The only translocations are the fusion of two acrocentrics in the ancestor to produce human chromosome 2 and a t(5;17) translocation in the gorilla lineage (Wienberg et al., 1990). A few examples of activation of neocentromeres have been observed (Dutrillaux, 1979). Inversions account for more than 90% of the rearrangements. FISH analysis with YAC clones has led to the identification of five of the six evolutionary pericentric inversion breakpoints in human chromosomes 4, 9, and 12 (Nickerson and Nelson, 1998). It is interesting, though not surprising, that some of the inversions induced by radiation are the same as those that have been fixed (that is, become homozygous) during evolution (Dutrillaux et al., 1986).

Chromosomal rearrangements that reproduce the ancestral state of a genome are called *reverse chromosomal mutations*, and quite a number of these have been identified. For example, a paracentric inv(7)(q11.2q22.1) chromosome has the same banding pattern as the corresponding gorilla chromosome (Haaf and Schmid, 1987). Chromosome 7 is especially prone to inversion, accounting for 20% of all published cases. This may reflect the presence of hotspots for rearrangement that may be conserved over long evolutionary periods. The human 22q11 region is such a hotspot, and so is the homologous region in the mouse (Puech et al., 1997).

Some of the human chromosomes have been more highly conserved than others. The X chromosome and autosomes 6, 8, 11, 12, 18, and 19 are the most highly conserved, being little changed from their homologues among Old World monkeys (Clemente et al., 1990). Chromosomes 1, 3, and 7 are the least conserved and the most likely to show changes after radiation. More surprising is

the evidence coming from comparisons with more distantly related species. The cat (2n = 38) and human (2n = 46) karyotypes obviously differ but nevertheless appear to have changed very little from their ancestral karyotype. Thus, the cat karyotype can be constructed from human chromosomes by postulating only seven chromosome breaks and one inversion (Rettenberger et al., 1995). A more comprehensive analysis including additional FISH mapping shows that human chromosome 11 is apparently identical to its cat homologue (O'Brien et al., 1997).

The origin of human chromosome 21 has been traced back 50 million years. It was formed after the divergence of platyrrhines (New World monkeys) and catarrhines (Old World monkeys, apes, and humans) but before the divergence of the Cercopithecidae (Old World monkeys) from apes and humans. Humans and Pongidae (great apes) have an equivalent chromosome 21, but in other catarrhines, a variety of translocations have produced quite different chromosomes. Only humans and Pongidae produce Down syndrome or its equivalent. The longer catarrhine and platyrrhine chromosomes containing human chromosome 21 material may be lethal when trisomic (Richard and Dutrillaux, 1998).

High-resolution banding and FISH mapping are excellent tools for evolutionary comparisons, but they do not detect the gross DNA differences between humans and great apes that are revealed by comparative genomic hybridization (Chapter 8) and interspecific representational difference analysis (Toder et al., 1998). Furthermore, they become increasingly unreliable as the evolutionary distance between species increases. Finer discrimination and greater reliability can be achieved using mapped genes and looking for regions of conserved synteny in species with fairly dense genetic maps, such as human and mouse (Ehrlich et al., 1997).

Evolution of the X and Y Chromosomes: Dosage Compensation

The mammalian sex chromosomes probably evolved from a pair of autosomes. One of the pair gained the male-determining *SRY* gene from the previous male-determining (proto-Y) chromosome and became the new Y chromosome, while its unchanged homologue became the X. During subsequent evolution, three further changes took place. Crossing over and recombination between X and Y was suppressed, most of the Y-linked genes were lost or inactivated by mutation, and a dosage compensation mechanism arose to equalize the expression levels

of X-linked genes in the two sexes. This involved inactivation of most of the genes on one of the two X chromosomes in females. Doubling the expression level of genes expressed only from the single active X chromosome in both males and females equalized the expression levels of X-linked and autosomal genes (Ohno, 1967; Graves et al., 1998).

Ohno (1967) pointed out that mammalian X inactivation had certain consequences regarding the movement of genes between X and autosomes. The movement of any gene that shows a dosage effect would be likely to produce deleterious effects because of the altered gene dosage. We would now stipulate "unless the gene is imprinted in its autosomal location." Thus, the gene content of the X chromosome would change very slowly and be fairly constant in all mammals. This is generally true, but with significant exceptions. In monotremes and marsupials, the X chromosome makes up only 3% of the haploid genome, while in placental mammals it is 5%. Comparative mapping studies have shown that the long arm and proximal short arm of the human X correspond to the prototherian (monotreme) and metatherian (marsupial) X, and thus presumably to the ancestral mammalian X chromosome. The rest of the short arm represents one or more autosomal regions that have been added more recently to the eutherian X. The fusion point of the ancestral rearrangement maps to human Xp11.23 (Wilcox et al., 1996). In time, most of these transferred genes became subject to X-inactivation and the remaining pseudoautosomal region became shorter (Fig. 30.2; Perry et al., 1998).

Interesting secondary adjustments have been made to permit the successful translocation of some autosomal genes to the X. For example, the pyruvate dehydrogenase E1α subunit (*PDHA*) gene is autosomal in marsupials but X-linked in placental (eutherian) mammals. A single copy of the gene is present in the marsupial genome, but eutherians have a second, testis-specific, intronless copy that arose by reverse transcriptase action and retrotransposition to an autosome, just as happened with the phosphoglycerate kinase (*PGK*) gene (Fitzgerald et al., 1996). Both these genes are essential. The inactivation of the single X chromosome in eutherian males during spermatogenesis inactivates the *PDHA* and *PGK* genes on the X, but activation of the autosomal copies in spermatocytes enables these cells to function normally.

The functionality of a gene can sometimes be restored by recombination between two nonfunctional alleles that have mutations in different parts of the gene. However, this cannot occur in the absence of recombination. The suppression of crossing over between X and Y should thus have led to to gradual loss of virtually all genes from the Y not essential for sex determination or male

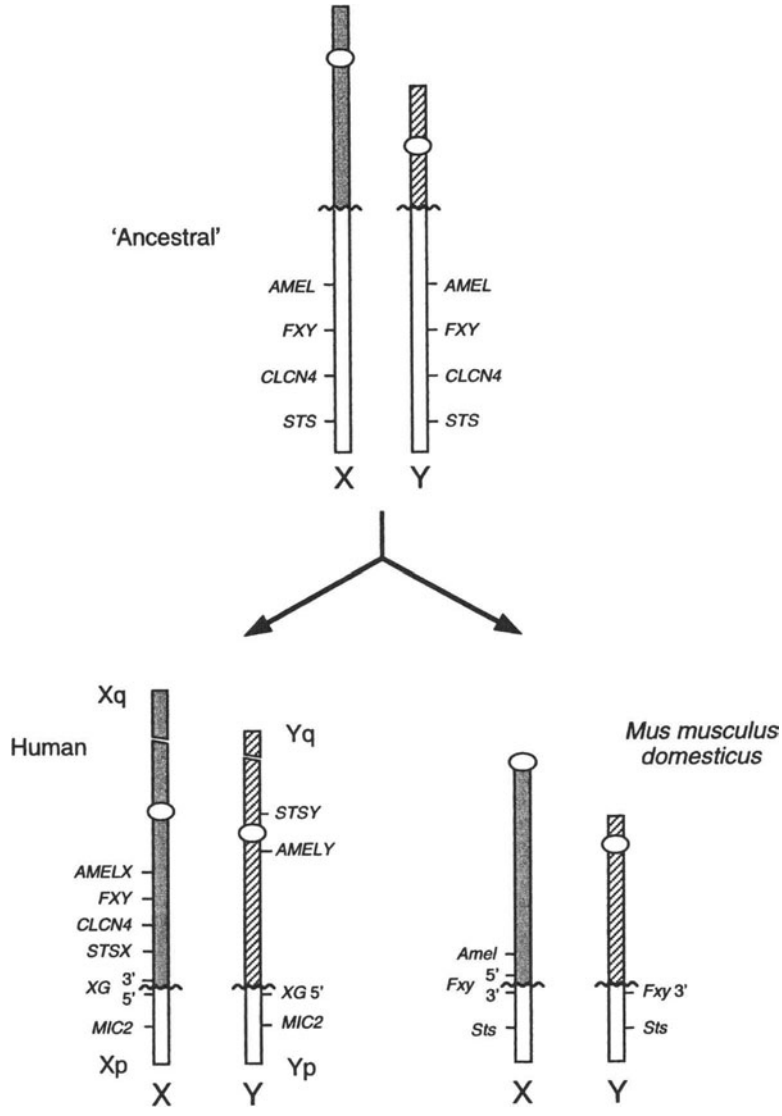

Figure 30.2. Model of the evolution of the human and mouse pseudoautosomal regions (PARs) on the X and Y chromosomes. The *XG* and *Fxy* genes span the pseudoautosomal boundaries (wavy lines) in humans and mice, respectively. X-unique (shaded) and Y-unique (hatched) regions are indicated (modified from Perry et al., 1998, Hum Mol Genet 7:299–305, with permission of Oxford University Press).

fertility. H. J. Muller pointed this out many years ago, and this phenomenon of inevitable gene degradation in the absence of recombination is referred to as *Muller's ratchet*. However, there is an interesting exception to this phenomenon: Some genes on the Y retain their function despite never crossing over with a homologue on the X. This includes several genes involved in male fertility.

The surprising feature of these genes involved in male fertility is that they are present in multiple copies on the Y. Since their deletion is associated with azoospermia, they are called *AZF* genes. *AZFb*, also known as *RBM*, was the first to be isolated. There are 20–50 *RBM* genes or pseudogenes scattered along both arms of the Y, with expression limited to the testis. The *AZFc* region on Yq contains the *DAZ* (deleted in azoospermia) multigene family, which is found only in Old World monkeys, apes, and humans. It appears to have arisen from the single-copy autosomal gene *DAZLA*, located at 3p24, which is expressed only in the germline of both testis and ovary and shares homology with *boule*, a gene whose mutation causes azoospermia in *Drosophila* (Agulnik et al., 1998). After transposition to the Y, *DAZ* underwent a complex series of duplications and rearrangements but remains as a cluster on Yq. This is deleted in 5–15% of infertile men with azoospermia, suggesting a functional role. Cooke and Elliott (1997) have suggested that the presence of multiple copies of these genes on the Y provides a means of forming normal copies from defective copies, by ectopic homologous recombination, thus enabling some Y-linked genes to escape Muller's ratchet.

In contrast to the relatively high level of conservation of the X chromosome, the mammalian Y chromosome shows remarkable diversity and rapid evolution among humans and higher primates, providing insights into human evolution and migration patterns. Most men worldwide have the same *DAZ* variants, supporting a recent (55,000–200,000 years ago) African origin of our species (Agulnik et al., 1998). The absence of significant variation in a 729-bp intron of the Y-linked *ZFY* gene in a worldwide sample of 38 males indicates either a very recent origin of our species, no more than about 270,000 years ago, or recurrent male population bottlenecks (Dorit et al., 1995). Comparative studies have shown that the present 2.6-Mb pseudoautosomal region on the short arm of X and Y chromosomes, PAR1, is only a remnant of a much larger pseudoautosomal region. For example, the ubiquitin activating enzyme (*UBE*) gene is present in the X-Y pairing segment in the platypus, a monotreme. It is not in that segment in marsupials or placental mammals, though it is still present on X and Y. The *UBE* gene is no longer on the Y in humans and other higher primates (Mitchell et al., 1998). Deterioration of genes on the Y chromosome is the

driving force in this loss, as it is in sex chromosome evolution in general (Graves et al., 1998).

The human X and Y chromosomes have many blocks of similar DNA sequence in common. Some of these are located on Xq21 and Yp, regions that do not recombine during meiosis. This led to the idea that an inversion occurred during the evolution of the Y. Lambson et al. (1992) have reviewed the interchanges that occurred between X and Y chromosomes over the last 80 million years. A 4-Mb block on Xq is homologous to noncontiguous segments on Yp, suggesting that the segment was transposed from Xq to Y and later disrupted by a Y inversion. Schwartz et al. (1998) sequenced the breakpoints of this inversion and found LINE1 sequence elements, suggesting that ectopic recombination had occurred between two LINE1 elements, one inverted with respect to the other, in an otherwise nonhomologous region (see Fig. 30.1 for another example of this). Comparison with other primates indicated that the X-Y transposition occurred after the divergence of hominid and chimpanzee lineages. The 99.3% nucleotide identity between the X and Y chromosome segments places the transposition about 3–4 million years ago. Gläser et al. (1997) used multicolor FISH to map eight genes in Xp22 to prometaphase chromosomes. While the order was highly conserved on the X chromosome in all hominoid primates tested, there was a complex series of rearrangements affecting their order on the Y chromosome.

Evolution of Telomeric and Centromeric Regions

The human genome, like those of other mammals and of birds, has evolved a highly nonrandom arrangement of gene-rich and gene-poor isochores and bands (Bernardi, 1995). The most gene-rich isochores lie close to the telomeres of most chromosomes, regions noted for their high recombination frequencies. They are also preferred sites of origin of multigene families, such as the olfactory receptor family (Trask et al., 1998), and the sites where most minisatellite repeat elements are generated. In fact, these subtelomeric regions are sites of marked genomic plasticity and appear to serve as nurseries for generating new genes and enhancing genetic diversity.

The pericentromeric regions, with their abundant heterochromatin, are also regions of high genomic plasticity. Analysis of the sequences flanking the centromere of chromosome 10 found high levels of duplication, transposition, inver-

sion, and deletion. Extrapolated to the whole 3400-Mb genome, perhaps 50 Mb of DNA in the regions closest to the centromeres is quite unstable (Jackson et al., 1999). These regions are preferred sites for integration or transposition of DNA sequences. Most of the transposed segments are truncated, nonexpressed pseudogenes, but some are complete genes. Eichler et al. (1997) described the duplication of a gene-rich cluster by transposition from Xq28 to the pericentromeric 16p11.1 region, a mechanism for genome evolution. They also observed transpositional duplication of a 9.7-kb segment of the adrenoleukodystrophy (ALD) gene from Xq28 into the pericentromeric regions of multiple chromosomes: 2p11, 10p11, 16p11, and 22q11. Their 92–96% sequence identity with the ALD gene indicates they probably arose only 5–10 million years ago, late in higher primate evolution.

Centromeres themselves appear to evolve rapidly. Most eukaryotic centromeres contain abundant repetitive sequences, but these vary markedly among species. Even within the human species, chromosome-specific variants of the centromeric α satellite are present on almost every chromosome (see Chapter 4). Neocentromeres also arise rather frequently, in evolutionary terms, by the sudden recruitment of totally different sequences. In humans, this is seen most frequently on the Y chromosome (Tyler-Smith et al., 1998).

References

Agulnik AI, Zharkikh A, Boettger-Tong H, et al. (1998) Evolution of the *DAZ* gene family suggests that Y-linked *DAZ* plays little, or a limited, role in spermatogenesis but underlines a recent African origin for human populations. Hum Mol Genet 7:1371–1377

Bernardi G (1995) The human genome: organization and evolutionary history. Annu Rev Genet 29:445–476

Clemente LC, Ponsa M, García M, et al. (1990) Evolution of the Simiiformes and the phylogeny of human chromosomes. Hum Genet 84: 493–506

Cooke HJ, Elliott DJ (1997) RNA-binding proteins and human male fertility. Trends Genet 13:87–89

Desouza AT, Yamada T, Mills JJ, et al. (1997) Imprinted genes in liver carcinogenesis. FASEB J 11:60–67

Doolittle RF (1998) Microbial genomes opened up. Nature 392:339–342

Dorit RL, Akashi H, Gilbert W (1995) Absence of polymorphism at the ZFY locus in the human Y chromosome. Science 268:1183–1185

Dorit RL, Schoenbach L, Gilbert W (1990) How big is the universe of exons? Science 250:1377–1382

Drummond, JT, Genschel J, Wolf E, et al. (1997) *DHFF/MSH3* amplification in methotrexate—resistant cells alters the hMutSα/Hmutsβ ratio and reduces the efficiency of base—base mismatch repair. Proc Natl Acad Sci USA 94:10144–10149

Dutrillaux B (1979) Chromosomal evolution in primates: tentative phylogeny for Microcebus murinus (Prosimian) to man. Hum Genet 48:251–314

Dutrillaux B, Couturier J, Sabatier L, et al. (1986) Inversions in evolution of man and closely related species. Ann Génét 29:195–202

Ehrlich J, Sankoff D, Nadeau JH (1997) Synteny conservation and chromosome rearrangements during mammalian evolution. Genetics 147:289–296

Eichler EE, Budarf ML, Rocchi M, et al. (1997) Interchromosomal duplications of the adrenoleukodystrophy locus: a phenomenon of pericentromeric plasticity. Hum Mol Genet 6:991–1002

Fitzgerald J, Wilcox SA, Graves JAM (1996) A eutherian X-linked gene, PDHA1, is autosomal in marsupials: a model for the evolution of a second, testis-specific variant in eutherian mammals. Genomics 18:636–642

Gläser B, Grützner F, Taylor K, et al. (1997) Comparative mapping of Xp22 genes in hominoids—evolutionary linear instability of their Y homologues. Chrom Res 5:167–176

Graves JAM, Disteche CM, Toder R (1998) Gene dosage in the evolution and function of mammalian sex chromosomes. Cytogenet Cell Genet 80:94–103

Haaf T, Schmid M (1987) Paracentric inversion in human chromosome 7 as a graphic example of reverse chromosome mutation. Hum Evol 2:321–327

Jackson MS, Rocchi M, Thompson G, et al. (1999). Sequences flanking the centromere of human chromosome 10 are a complex patchwork of arm-specific sequences, stable duplications and unstable sequences with

homologies to telomeric and other centromeric locations. Hum Mol Genet 8:205–215

Kelley MJ, Peck M, Seuanez HN, et al. (1992) Emergence of the keratinocyte growth factor multigene family during the great ape radiation. Proc Natl Acad Sci USA 89:9287–9291

Lambson B, Afara N, Mitchell M, et al. (1992) Evolution of DNA sequence homologies between the sex chromosomes in primate species. Genomics 14:1032–1040

Lundquist E, Johansson I, Ingelman-Sundberg M (1999) Genetic mechanisms for duplication and multiduplication of the CYP2D6 gene and methods for detection of duplicated CYP2D6 genes. Gene 226:327–338

Lupski JR (1998) Genomic disorders: structural features of the genome can lead to DNA rearrangements and human disease traits. Trends Genet 14:417–422

Maleszka R, Couet HG de, Miklos GLK (1998) Data transferability from model organisms to human beings: Insights from the functional genomics of the flightless region of Drosophila. Proc Natl Acad Sci USA 95: 3731–3736

Mitchell MJ, Wilcox SA, Watson JM, et al. (1998) The origin and loss of the ubiquitin activating enzyme gene on the mammalian Y chromosome. Hum Mol Genet 7:429–434

Moran JV, DeBerardinis RJ, Kazazian HH Jr (1999) Exon shuffling by L1 retrotransposition. Science 283:1530–1534

Nadeau JH, Sankoff D (1997) Comparable rates of gene loss and functional divergence after genome duplications early in vertebrate evolution. Genetics 147:1259–1266

Nickerson E, Nelson DL (1998) Molecular definition of pericentric inversion breakpoints occurring during the evolution of humans and chimpanzees. Genomics 50:368–372

O'Brien SJ, Wienberg J, Lyons LA (1997) Comparative genomics: lessons from cats. Trends Genet 13:393–399

Ohno S (1967) Sex chromosomes and sex-linked genes. Springer-verlag, New York.

O'Neill RJW, O'Neill MJ, Graves JAM (1998) Undermethylation associated with retroelement activation and chromosome remodelling in an interspecific mammalian hybrid. Nature 393:68–72

Perry J, Feather S, Smith A, et al. (1998) The human *FXY* gene is located within Xp22.3: implications for evolution of the mammalian X chromosome. Hum Mol Genet 7:299–305

Puech A, Saint-Jore B, Funke B, et al. (1997) Comparative mapping of the human 22q11 chromosomal region and the orthologous region in mice reveals complex changes in gene organization. Proc Natl Acad Sci USA 94: 14608–14613

Rettenberger G, Klett Ch, Zechner U, et al. (1995) ZOO-FISH analyses: cat and human karyotypes closely resemble the putative ancestral mammalian karyotype. Chrom Res 3:479–486

Richard F, Dutrillaux B (1998) Origin of human chromosome 21 and its consequences: a 50-million-year-old story. Chrom Res 6:263–268

Schwartz A, Chan DC, Brown LC, et al. (1998) Reconstructing hominid Y evolution: X-homologous block, created by X-Y transposition, was disrupted by Yp inversion through LINE-LINE recombination. Hum Mol Genet 7:1–11

Small K, Iber J, Warren ST (1997) Emerin deletion reveals a common X-chromosome inversion mediated by inverted repeats. Nat Genet 16:96–99

Strissel PL, Dann HA, Pomykala HM, et al. (1998) Scaffold-associated regions in the human type I interferon gene cluster on the short arm of chromosome 9. Genomics 47:217–229

The *C. elegans* Sequencing Consortium (1998) Genome sequence of the nematode *C. elegans*: a platform for investigating biology. Science 282:2012–2018

Toder R, Xia Y, Bausch E (1998) Interspecies comparative genome hybridization and interspecies representational difference analysis reveal gross DNA differences between humans and great apes. Chrom Res 6:487–494

Trask BJ, Friedman C, Martin-Gallardo A, et al. (1998) Members of the olfactory receptor gene family are contained in large blocks of DNA duplicated polymorphically near the ends of human chromosomes. Hum Mol Genet 7:13–26

Tyler-Smith C, Corish P, Burms E (1998) Neocentromeres, the Y chromosome and centromere evolution. Chrom Res 6:65–71

Wienberg J, Jauch A, Stanyon R, et al. (1990) Molecular cytotaxonomy of primates by chromosomal *in situ* suppression hybridization. Genomics 8:347–350

Wilcox SA, Watson JM, Spencer JA, et al. (1996) Comparative mapping identifies the fusion point of an ancient mammalian X-autosomal rearrangement. Genomics 35:66–70

Yoder JA, Walsh CP, Bestor TH (1997) Cytosine methylation and the ecology of intragenomic parasites. Trends Genet 13:335–340