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REVIEW
Chromosomal Duplications in Bacteria, Fruit Flies, and Humans

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Tandem duplication of chromosomal segments has been recognized as a frequent mutational mechanism in several genetic model systems. In bacteria, fruit flies, and humans, duplications form by similar molecular mechanisms and appear to be important in genome evolution.

General Features

A tandem duplication does not cause the host to lose expression of any genetic information, as long as the duplicated segment is not included entirely within a single functional genetic element or gene. As there is no net loss of genetic information, duplications are essentially unrestricted in size and location on the chromosome. The phenotype resulting from a duplication mutation may be due to the increase in gene dosage, which usually causes a gain-of-function, or to the functional consequences of a new sequence element found at the junction point. DNA duplication may also affect folding of the chromosome and thus could have wide-ranging indirect effects on phenotype. The large number of potential exchanges that may yield duplication mutations and the high probability that these mutants will be viable suggest that duplications will be a large fraction of detected mutation whenever appropriate selection conditions are used (Roth et al., in press).

Duplications within the Bacterial Chromosome

Possibly the first report of bacterial duplications was that of Horiuchi et al. (1963); they reported duplications of the *lac* operon isolated following selection for faster growth on lactose. The basic genetic properties of duplications in bacteria were first outlined by Campbell (1963, 1965), using duplications of the *gal* region. These and other early work on genetics of duplications have been reviewed by Anderson and Roth (1977) and more recently by Petes and Hill (1988) and by Roth et al. (in press). Genetic studies of the haploid unicellular bacterium *Salmonella typhimurium* demonstrate that in an unselected culture the frequency of duplication of particular loci varies from 3% to $\sim 10^{-5}$, and an average locus is duplicated in ~1 in every 1,000 cells. It is estimated that nearly 10% of the cells in an unselected culture carry a duplication of some region of the chromosome. Considered together with the instability of duplication as evidenced by segregation analysis, these estimates suggest that the bacterial chromosome is in a constant state of flux and that duplications are continually acquired and lost (Anderson et al. 1976; Anderson and Roth 1977, 1978, 1979, 1981; Roth et al., in press). Tandem chromosomal duplications have also been identified by genetic analysis in *Escherichia coli* where mild UV irradiation causes a large increase in duplication frequency (Hill and Combriato 1973; Hill et al. 1977).

A physical analysis of chromosomal duplications in the *lac* region of *E. coli* reveals a basal frequency of 0.7%; this confirms the observation that tandem duplications are present at a surprisingly high frequency in bacterial populations (Heath and Weinstock 1991). Following UV irradiation, 12% of survivors have duplication of the *lac* region, a 16-fold increase over the basal level (Heath 1992). If all regions of the bacterial chromosome form duplications of similar size and frequency as the *lac* region, it is likely that every cell surviving mild UV irradiation carries a duplication of one or more portions of its chromosome. Further studies of different regions of the *E. coli* chromosome indicate that duplications occur at a frequency of 10^{-4} to 10^{-3} and are stimulated at least tenfold in most regions by relatively mild UV irradiation (Heath 1992). The spontaneous tandem duplication frequency of the *metE* locus in an *E. coli* mismatch repair mutant, *mutL*, increased sixfold over the frequency observed in a wild-type strain, indicating that mismatch repair stabilizes the chromosome and maintains gene dosage (Heath 1992).

Physical measurements of *E. coli* chromosomal duplications by pulsed-field gel electrophoresis (PFGE) reveal that they are very large and range from 140 kb to at least 2,100 kb (Heath 1992; Weinstock 1994), the larger

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duplication measuring about one-half of the ~5.0-Mb *E. coli* chromosome (Heath 1992).

Genetic and physical mapping of bacterial duplication end points demonstrates a nonrandom distribution. The chromosomal region duplicated is flanked by a large sequence repeat in direct orientation. The known repeated sequences that appear to be major contributors to chromosomal duplication formation include ribosomal RNA (*rrn*) operons (Hill et al. 1977; Anderson and Roth 1981) and other repeated genes (Petes and Hill 1988), the recombination hotspot (Rhs) element (Lin et al. 1984), insertion sequence (IS) elements, and transposons (Chumley and Roth 1980; Heath 1992; Haack and Roth, in press). It is interesting that the seven *E. coli rrn* operons are not used equivalently for duplication formation, suggesting that higher-order chromosome structure, or slight variation in the DNA sequence of recombined sequences, may influence the frequency of duplication (Heath 1992).

The generally accepted model for the formation of chromosomal duplication in bacteria is that, after chromosomal replication, misaligned repeated sequences (e.g., *rrn* operons, IS elements, transposons) act as regions of homology or substrates for homologous recombination, leading to duplication or deletion of the specific region between the repeated sequences. Since these repeats are usually far apart on the chromosome, duplications are large and the corresponding deletions may not be recovered, since they remove essential genes. A variety of long sequence repeats probably serve as substrates for homologous recombination at frequencies that reflect the length of the repeat and the degree of sequence similarity (Roth et al., in press). Support for the idea that most duplications form by recombination between repeated sequences is that duplication formation is found generally to be highly dependent on the RecA function, a protein essential for homologous recombination. In addition, the observation that DNA-damaging treatment increases formation of duplications is not surprising in view of the well-known stimulation of homologous recombination by DNA damage (Heath 1992).

In principle, a single reciprocal exchange between separated sequence repeats in sister chromosomes would simultaneously generate a duplication in one sister chromosome and deletion in the other sister. Using regions in which both duplication and deletion recombinants are fully viable, it is possible to examine for the coincidence of such products. Selected duplications are seldom found to be accompanied by the corresponding deletions in cells of the same clone. This suggests that sister chromosome exchanges in bacteria are seldom reciprocal (M. Carter, T. Galiski, J. Roth, unpublished data).

The high frequency formation and rapid loss of duplications through segregation under nonselective conditions suggest that chromosomal duplication may be a mechanism by which bacteria can amplify particular functions and thereby adapt to stressful conditions in nature without undergoing irreversible changes in their genomes (Sonti and Roth 1989). Chromosomal duplications may provide the increased gene dosage of a required allele, may provide a novel operon fusion at the join point, or may supply redundant DNA for genetic divergence (Anderson and Roth 1978).

Drosophila Duplications

A chromosomal duplication was first identified in the fruit fly *Drosophila melanogaster* at the *Bar* locus. Tice (1914) identified a male *D. melanogaster* that had narrow eyes and called the phenotype "bar." The bar character reverted at a high frequency, was semidominant, and was found to depend on a sex-linked gene. The *Bar* mutation occurred at a high frequency and was demonstrated by genetic analysis with flanking markers to result from unequal crossing-over. It was proposed as a new kind of "section mutation," in contradistinction to point mutations, gene mutations, or those mutations or inherited changes that included whole chromosomes, such as nondisjunction or tetraploidy (Sturtevant 1924).

Examination of salivary gland polytene chromosomes from *Bar* flies identified a tandem duplication of seven bands of the 16A1-16A7 section of the X-chromosome (Bridges 1936). Double-*Bar* was associated with triplication of this region, while *Bar* reverted had lost the tandem duplication under direct microscopic evaluation of polytene chromosomes. It was proposed that (*a*) the source of the *Bar* duplication was the material directly adjacent to the repeat and that (*b*) the phenotype results from the effect of increasing the action of certain genes by doubling their number (Bridges 1936). Subsequent molecular analyses demonstrated a transposable element (B104) flanking the region duplicated. DNA sequence analysis of the junction of the B104 element supported a model whereby the *Bar* duplication was generated by a homologous recombination event between one B104 element in region 16A1 and another in region 16A7 (Tsubota et al. 1989, 1991).

The phenotype conveyed by the *Bar* duplication appears to result from a gene dosage effect of *BarH1* and/or *BarH2*, apparently redundant homeobox genes mapping within the duplication, whose overexpression was found to be capable of inducing *Bar*-like eye malformation (Higashijima et al. 1992; Kojima et al. 1991, 1993).

The *white* eye locus on the X-chromosome and the *rosy* locus on chromosome 3 are additional regions where spontaneous, frequently occurring, unequal exchange have been identified at unexpectedly high frequencies (Judd et al. 1961*a*, 1961*b*; Green 1959, 1961;

Gelbart and Chovnick 1979). At the *rosy* locus an unequal crossing-over event has been estimated to occur at a frequency of 1 in every 500 female meioses and has been proposed to explain complications in the genetic analysis (Gelbart and Chovnick 1979). Subsequent molecular analysis of the *white* locus has demonstrated that repeat sequences, a *copia*-like element for some alleles and a retrovirus-like transposon *roo* for other alleles, are found at the rearrangement breakpoints (Davis et al. 1987; Goldberg et al. 1983).

Human Disease Phenotypes Resulting from Chromosomal Duplication

Asymmetrical exchanges that generate duplications and deficiencies within tandem arrays of related genes occur frequently in the human genome and are responsible for common clinical phenotypes. Globin-chain variants and hemoglobinopathies, (Baglioni et al. 1962; Goosens et al. 1980), the visual pigment genes and variation in color vision (Nathans et al. 1986; Nathans 1994), and a chimeric 11β-hydroxylase synthase gene responsible for hypertension secondary to glucocorticoid-remediable aldosteronism (Lifton et al. 1992) serve as well-documented examples. The disease phenotype may be elicited by simple changes in gene dosage of a gene that lies between the flanking repeat sequences, where recombination occurs without alteration of gene sequences, as exemplified by the peripheral neuropathies Charcot-Marie-Tooth (CMT) disease and Hereditary neuropathy with liability to pressure palsies (HNPP) (Roa and Lupski 1994).

CMT disease is a common inherited peripheral neuropathy occurring in ~1 in 2,500 individuals. Although genetically heterogeneous, some 70% of inherited (Wise et al. 1993) and 90% of de novo (Hoogendijck et al. 1992) type 1 CMT cases have a tandem duplication of a 1.5-Mb region in human chromosome 17p11.2-p12 that is transmitted in a stable manner (Lupski et al. 1991, 1993; Raeymaekers et al. 1991; Pentao et al. 1992; Wise et al. 1993; Patel and Lupski 1994). The failure to recognize the molecular duplication can lead to misinterpretation of marker genotypes for affected individuals, identification of false recombinants, and incorrect localization of the disease locus by genetic mapping (Lupski et al. 1991; Lupski 1992). It is interesting that the de novo CMT1A duplication appears to originate exclusively during male gametogenesis (Palau et al. 1993; Wise et al. 1993; Hertz et al. 1994).

The normal chromosome 17 contains two copies of an ~30-kb repeat sequence (CMT1A-REP) flanking the 1.5-Mb CMT1A region in direct tandem orientation. In contrast, CMT1A-REP is present in three copies on the duplicated chromosome. Physical analysis with PFGE to separate large chromosome fragments and Southern blotting with probes to CMT1A-REP can identify CMT1A duplication–specific junction fragments (Pentao et al. 1992). In addition to the CMT1A duplication, a reciprocal recombination event is responsible for the corresponding 1.5-Mb deletion that is associated with HNPP, a clinically distinct neuropathy (Chance et al. 1993, 1994). Multiple unrelated individuals with either CMT1A or HNPP, of different ethnicities have similar junction fragments, suggesting a precise recombination event involving CMT1A-REP (Wise et al. 1993; Lorenzetti et al. 1995).

The identification of rare individuals with both chromosome 17p partial trisomy encompassing the CMT1A locus and the CMT1 phenotype supports a gene dosage model wherein trisomic overexpression of a gene located within the CMT1A duplication is responsible for the CMT1 phenotype (Chance et al. 1992; Lupski et al. 1992; Roa et al. 1993*d*, and in press). Mapping of the peripheral myelin protein gene *PMP22* within the CMT1A duplication supports the notion that *PMP22* is the dosage-sensitive gene (Matsunami et al. 1992; Patel et al. 1992; Timmerman et al. 1992; Valentijn et al. 1992*b*). Furthermore, identification of *PMP22* point mutations in rare nonduplication CMT1 patients confirmed that *PMP22* is the gene primarily responsible for CMT1A (Valentijn et al. 1992*a*; Roa et al. 1993*a*, 1993*b*, 1993*c*). The *PMP22* gene is contained within the reduced critical region of 460 kb defined by a rare alternative CMT1A duplication of smaller size (Valentijn et al. 1993). On the other hand, deletion of the 1.5-Mb region that results in decreased gene dosage of *PMP22* is associated with HNPP (Chance et al. 1993). The identification of a *PMP22* nonsense codon mutation leading to loss-of-function in PMP22 in rare HNPP patients without the 1.5-Mb deletion supports the hypothesis that *PMP22* underexpression results in HNPP (Nicholson et al. 1994).

Common Features of Chromosomal Duplications

Evaluations of duplications in bacteria, fruit flies and humans identify some common features: (*a*) Chromosomal duplication is a high frequency mutational event; (*b*) duplication may involve large chromosomal regions on the order of megabases; and (*c*) the region to be duplicated is flanked by repeat sequences in a direct orientation. These flanking sequences can be related genes, transposable elements, or other repeated sequences, that act as a substrate for unequal crossing-over by homologous recombination or asymmetric non–sister chromatid exchanges. Since the genome has numerous repeated sequences, the cell must possess some control mechanism to monitor unequal crossing-over in order to prevent a chromosome from recombining itself to pieces. (*d*) The reciprocal recombination product of

an unequal exchange results in a corresponding deletion of the region flanked by the repeat sequence. Detectable duplication would therefore be expected to be more common than deletion, since only small deletions not encompassing an essential gene would presumably be viable (Roth et al., in press). (*e*) Chromosomal duplications are reversible mutations; and (*f*) chromosomal duplications may complicate genetic mapping and the analysis of recombinants (Lupski et al. 1991, 1992; Matise et al. 1994; Gelbart and Chovnick 1979).

Implications for Human Disease

Given the high frequency of chromosomal duplications in several model systems studied, DNA duplications or "section mutations" (Sturtevant 1924) may be more frequent mutational events at some loci than are structural gene alterations. A disease phenotype resulting from such events may be at a single locus but may involve several genes. However, the phenotype would segregate in a Mendelian fashion as do those caused by mutations within a single gene.

The inherited peripheral neuropathies CMT1A and HNPP may be considered as "genomic diseases" in the sense that no coding sequence or protein has been altered but the genome has changed. The mutational mechanism is a function of intrinsic structural features located at the 17p11.2-p12 region of the human genome and may be the consequence of genome plasticity. Additional genetic disorders are likely to be shown to arise from recombination events mediated by specific structural features of the human genome and to be thought of as "genomic diseases" (Roa and Lupski 1994). The de novo and inherited deletions of the human chromosome 5q13 region that occur on both chromosome homologues and that are associated with autosomal recessive spinal muscular atrophies (Melki et al. 1994; the inversions that disrupt the factor VIII gene causing X-linked severe hemophilia (Lakich et al. 1993; Rossiter et al. 1994); and the deletions associated with the contiguous gene syndrome in Xp22.3 associated with Kallman syndrome and/or ichthyosis due to steroid sulfatase deficiency (Ballabio et al. 1990) are each examples of such genomic diseases.

The studies of DNA duplication in CMT1A and the reciprocal deletion in HNPP have delineated the concept of a "gene expression window" for a dosage-sensitive gene. Increased *PMP22* expression results in CMT1A, while decreased *PMP22* expression results in HNPP. The work on dup(17p) and CMT1A patients has blurred the artificial boundaries that separate chromosome syndromes from "single gene" disorders that segregate in a Mendelian fashion (Roa et al. 1993*d*; Roa and Lupski 1994). These latter studies also suggest that the clinical phenotype in chromosome aneuploidy syndromes considered to be a consequence of gene dosage effects (Epstein 1986) may actually result from effects of a small subset of dosage-sensitive genes mapping within the region of aneuploidy.

Unique structural features of the human genome predispose to unequal-crossing-over mutational events. If unequal-crossing-over events causing human disease occur only during meiotic recombination, then new mutation individuals will be nonmosaic. However, homologous recombination and unequal crossing-over may not be restricted to gametogenesis. If recombination occurs in somatic cells, then loss of heterozygosity secondary to deletion may result from unequal crossing-over. This could be responsible for somatic alterations leading to carcinogenesis. Hereditary nonpolyposis colon cancer (HNPCC) results from mutation in genes involved in mismatch repair. Chromosome duplications may be more frequent in HNPCC patients as in *E. coli mutL* strains (Heath 1992) and, further, may contribute to the multistep carcinogesis process.

Conclusions

Tandem chromosomal duplication as a mutational mechanism has been recognized for almost 60 years (Bridges 1936). The molecular mechanisms and frequency of such duplications and their involvement in genome evolution have been elucidated only in recent years. The biology of chromosomal duplication is remarkably similar in organisms as diverse as bacteria and humans and likely reflects specific structural features of the genomes. Similar mechanisms involving flanking repeat sequences may underlie the DNA rearrangements associated with contiguous-gene-deletion syndromes (Schmickel 1986; Ledbetter and Ballabio 1995). Chromosomal duplication and resultant gene duplication are ubiquitous features of genome evolution and have been viewed as the predominant mechanisms for the evolution of new gene functions and adaptive responses (Ohno 1970; Li and Graur 1991). Future studies are likely to identify chromosomal duplications as the molecular mechanism underlying other common traits.

References

Anderson RP, Miller CG, Roth JR (1976) Tandem duplications of the histidine operon observed following generalized transduction in *Salmonella typhimurium.* J Mol Biol 105:201–218

Anderson RP, Roth JR (1977) Tandem genetic duplications in phage and bacteria. Ann Rev Microbiol 31:473–505

——— (1978) Tandem chromosomal duplications in *Salmonella typhimurium:* fusion of histidine genes to novel promoters. J Mol Biol 119:147–166

——— (1979) Gene duplication in bacteria: alteration of gene

dosage by sister-chromosome exchanges. Cold Spring Harb Symp Quant Biol 43:1083–1087

——— (1981) Spontaneous tandem genetic duplications in *Salmonella typhimurium* arise by unequal recombination between rRNA (*rrn*) cistrons. Proc Natl Acad Sci USA 78:3113–3117

Baglioni C (1962) The fusion of two peptide chains in hemoglobin Lepore and its interpretation as a genetic deletion. Proc Natl Acad Sci USA 48:1880–1886

Ballabio A, Bardoni B, Guioli S, Basler E, Camerino G (1990) Two families of low-copy-number repeats are interspersed on Xp22.3: implications for the high frequency of deletions in this region. Genomics 8:263–270

Bridges CB (1936) The bar "gene" a duplication. Science 83:210–211

Campbell A (1963) Segregants from lysogenic heterogenotes carrying recombinant lambda prophages. Virology 20:344–356

——— (1965) The steric effect in lysogenization by bacteriophage lambda. 1. Lysogenization of a partially diploid strain of *Escherichia coli K12*. Virology 27:329–339

Chance PF, Abbas N, Lensch MW, Pentao L, Roa BB, Patel PI, Lupski JR (1994) Two autosomal dominant neuropathies result from reciprocal DNA duplication/deletion of a region on chromosome 17. Hum Mol Genet 3:223–228

Chance PF, Alderson MK, Leppig KA, Lensch MW, Matsunami N, Smith B, Swanson PD, et al (1993) DNA deletion associated with hereditary neuropathy with liability to pressure palsies. Cell 72:143–151

Chance PF, Bird TD, Matsunami N, Lensch M, Brothman AR, Feldman GM (1992) Trisomy 17p associated with Charcot-Marie-Tooth neuropathy type 1A phenotype: evidence for gene dosage as a mechanism in CMT1A. Neurology 42:2295–2299

Chumley FG, Roth JR (1980) Rearrangement of the bacterial chromosome using Tn*10* as a region of homology. Genetics 94:1–14

Davis PS, Shen MW, Judd BH (1987) Asymmetrical pairings of transposons in and proximal to the white locus of *Drosophila* account for four classes of regularly occurring exchange products. Proc Natl Acad Sci USA 84:174–178

Epstein CJ (1986) The consequences of chromosome imbalance: principles, mechanisms, and models. Cambridge University Press, Cambridge

Gelbart WM, Chovnick A (1979) Spontaneous unequal exchange in the rosy region of *Drosophila melanogaster*. Genetics 92:849–859

Goldberg ML, Sheen J-Y, Gehring WJ, Green MM (1983) Unequal crossing-over associated with asymmetrical synapsis between nomadic elements in the *Drosophila melanogaster* genome. Proc Natl Acad Sci USA 80:5017–5021

Goossens M, Dozy AM, Embury SH, Zachariades Z, Hadjiminas MG, Stamatoyannopoulos G, Kan YW (1980) Triplicated α-globin loci in humans. Proc Natl Acad Sci USA 77:518– 521

Green MM (1959) Non-homologous pairing and crossing-over in *Drosophila melanogaster*. Genetics 44:1243–1256

——— (1961) Further data on non-homologous pairing and crossing over in *Drosophila melanogaster*. Genetics 46:1555–1560

Haack KR, Roth JR. Recombination between chromosomal IS200 elements supports frequent duplication formation in *Salmonella typhimurium*. Genetics (in press)

Heath JD (1992) Control of chromosomal rearrangements in *Escherichia coli*. PhD thesis, University of Texas Health Science Center, Houston

Heath JD, Weinstock GM (1991) Tandem duplications of the *lac* region of the *Escherichia coli* chromosome. Biochimie 73:343–352

Hertz JM, Børglum AD, Brandt CA, Flint T, Bisgaard C (1994) Charcot-Marie-Tooth disease type 1A: the parental origin of a *de novo* 17p11.2-p12 duplication. Clin Genet 46:291–294

Higashijima S, Kojima T, Michiue T, Ishimaru S, Emori Y, Saigo K (1992) Dual *Bar* homeobox genes of *Drosophila* required in two photoreceptor cells, R1 and R6, and primary pigment cells for normal eye development. Genes Dev 6:50–60

Hill CW, Combriato G (1973) Genetic duplications induced at very high frequency by ultraviolet irradiation in *Escherichia coli*. Mol Gen Genet 127:197–214

Hill W, Grafstrom RH, Harnish BW, Hillman BS (1977) Tandem duplications resulting from recombination between ribosomal RNA genes in *Escherichia coli*. J Mol Biol 116:407–428

Hoogendijk JE, Hensels GW, Gabreels-Festen AAWM, Gabreels FJM, Janssen EAM, De Jonghe P, Martin J-J, et al (1992) *De novo* mutation in hereditary motor and sensory neuropathy type 1. Lancet 339:1081–1082

Horiuchi R, Horiuchi S, Novick A (1963) The genetic basis of hypersynthesis of β-galactosidase. Genetics 48:157–169

Judd BH (1961*a*) Analysis of products from regularly occurring asymmetrical exchange in *Drosophila melanogaster*. Genetics 46:1687–1697

——— (1961*b*) Formation of duplication-deficiency products by asymmetrical exchange within a complex locus of *Drosophila melanogaster*. Proc Natl Acad Sci USA 47:545–550

Kojima T, Ishimaru S, Higashijima S-I, Takayama E, Akimaru H, Sone M, Emori Y, et al (1991) Identification of a different-type homeobox gene, *BarH1*, possibly causing Bar(*B*) and *Om(1D)* mutations in *Drosophila*. Genetics 88:4343–4347

Kojima T, Sone M, Michiue T, Saigo K (1993) Mechanism of induction of *Bar*-like eye malformation by transient overexpression of *Bar* homeobox genes in *Drosophila melanogaster*. Genetica 88:85–91

Lakich D, Kazazian HH, Antonarakis SE, Gitschier J (1993) Inversions disrupting the factor VIII gene are a common cause of severe haemophilia A. Nat Genet 5:236–241

Ledbetter DH, Ballabio A (1995) Molecular cytogenetics of contiguous gene syndromes: mechanisms and consequences of gene dosage imbalance. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease, 7th ed. McGraw-Hill, New York, pp 811–839

Li W-H, Graur D (1991) Fundamentals of molecular evolution. Sinauer, Sunderland, MA

Lifton RP, Dluhy RG, Powers M, Rich GM, Cook S, Ulick S, Lalouel J-M (1992) A chimaeric 11β-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature 355:262–265

Lin RJ, Capage M, Hill CW (1984) A repetitive DNA sequence *rhs,* responsible for duplications within the *Escherichia coli* K-12 chromosome. J Mol Biol 177:1–18

Lorenzetti D, Pareyson D, Sghirlanzoni A, Roa BB, Abbas NE, Pandolfo M, Di Donato S, Lupski JR (1995) A 1.5-Mb deletion in 17p11.2-p12 is frequently observed in Italian families with hereditary neuropathy with liability to pressure palsies. Am J Hum Genet 56:91–98

Lupski JR (1992) An inherited DNA rearrangement and gene dosage effect are responsible for the most common autosomal dominant peripheral neuropathy: Charcot-Marie-Tooth disease type 1A. Clin Res 40:645–652

Lupski JR, Chance PF, Garcia CA (1993) Inherited primary peripheral neuropathies: molecular genetics and clinical implications of CMT1A and HNPP. JAMA 270:2326–2330

Lupski JR, Montes de Oca-Luna R, Slaugenhaupt S, Pentao L, Guzzetta V, Trask BJ, Saucedo-Cardenas O, et al (1991) DNA duplication associated with Charcot-Marie-Tooth disease type 1A. Cell 66:219–232

Lupski JR, Pentao L, Williams LL, Patel PI (1993) Stable inheritance of the CMT1A DNA duplication in two patients with CMT1 and NF1. Am J Med Genet 45:92–96

Lupski JR, Wise CA, Kuwano A, Parke JT, Glaze DG, Ledbetter DH, Greenberg F, et al (1992) Gene dosage is a mechanism for Charcot-Marie-Tooth disease type 1A. Nat Genet 1:29–33

Matise TC, Chakravarti A, Patel PI, Lupski JR, Nelis E, Timmerman V, Van Broeckhoven C, et al (1994) Detection of tandem duplications and implications for linkage analysis. Am J Hum Genet 54:1110–1121

Matsunami N, Smith B, Ballard L, Lensch MW, Robertson M, Albertsen H, Hanemann CO, et al (1992) Peripheral myelin protein-22 gene maps in the duplication in chromosome 17p11.2 associated with Charcot-Marie-Tooth 1A. Nat Genet 1:176–179

Melki J, Lefebvre S, Burglen L, Burglen L, Burlet P, Clermont O, Millasseau P, et al (1994) *De novo* and inherited deletions of the 5q13 region in spinal muscular atrophies. Science 264:1474–1477

Nathans J (1994) In the eye of the beholder: visual pigments and inherited variation in human vision. Cell 78:357–360

Nathans J, Piantanida TP, Eddy RI, Shows TB, Hogness DS (1986) Molecular genetics of inherited variation in human color vision. Science 232:203–210

Nicholson GA, Valentijn LJ, Cherryson AK, Kennerson ML, Bragg TL, De Kroon RM, Ross DA, et al (1994) A frame shift mutation in the *PMP22* gene in hereditary neuropathy with liability to pressure palsies. Nat Genet 6:263–266

Ohno S (1970) Evolution by gene duplication. Springer, Berlin

Palau F, Lofgren A, De Jonghe P, Bort S, Nelis E, Sevilla T, Martin JJ, et al (1993) Origin of the *de novo* duplication in Charcot-Marie-Tooth disease type 1A: unequal nonsister chromatid exchange during spermatogenesis. Hum Mol Genet 2:2031–2035

Patel PI, Lupski JR (1994) Charcot-Marie-Tooth disease: a new paradigm for the mechanism of inherited disease. Trends Genet 10:128–133

Patel PI, Roa BB, Welcher AA, Schoener-Scott R, Trask BJ, Pentao L, Snipes GJ, et al (1992) The gene for the peripheral myelin protein *PMP-22* is a candidate for Charcot-Marie-Tooth disease type 1A. Nat Genet 1:159–165

Pentao L, Wise CA, Chinault AC, Patel PI, Lupski JR (1992) Charcot-Marie-Tooth type 1A duplication appears to arise from recombination at repeat sequences flanking the 1.5 Mb monomer unit. Nat Genet 2:292–300

Petes TD, Hill CW (1988) Recombination between repeated genes in microorganisms. Annu Rev Genet 22:147–168

Raeymaekers P, Timmeraman V, Nelis E, De Johnge P, Hoogendijk JE, Baas, F, Barker DF, et al (1991) Duplication in chromosome 17p11.2 in Charcot-Marie-Tooth neuropathy type 1a (CMT1A). Neuromuscul Disord 2:93–97

Roa BB, Dyck PJ, Marks HG, Chance PF, Lupski JR (1993*a*) Dejerine-Sottas syndrome associated with point mutation in the peripheral myelin protein 22 (*PMP22*) gene. Nat Genet 5:269–273

Roa BB, Garcia CA, Pentao L, Killian JM, Trask BJ, Suter U, Snipes GJ, et al (1993*b*) Evidence for a recessive *PMP22* point mutation in Charcot-Marie-Tooth disease type 1A. Nat Genet 5:189–194

Roa BB, Garcia CA, Suter U, Kulpa DA, Wise CA, Mueller J, Welcher AA, et al (1993*c*) Charcot-Marie-Tooth disease type 1A: Association with a spontaneous point mutation in the *PMP22* gene. N Engl J Med 329:96–101

Roa BB, Garcia CA, Wise CA, Anderson K, Greenberg F, Patel PI, Lupski JR (1993*d*) Gene dosage as a mechanism for a common autosomal dominant peripheral neuropathy: Charcot-Marie-Tooth disease type 1A. In: Epstein CJ (ed) The phenotypic mapping of Down syndrome and other aneuploid conditions. Vol 384 in: Progress in clinical and biological research. Wiley-Liss, New York, pp 187–205

Roa BB, Greenberg F, Gunaratne P, Sauer CM, Lubinsky MS, Kozma C, Meck JM, et al. Duplication of the *PMP22* gene in 17p partial trisomy patients with Charcot-Marie-Tooth type 1A neuropathy. Hum Genet (in press)

Roa BB, Lupski JR (1994) Molecular Genetics of Charcot-Marie-Tooth neuropathy. In: Harris H, Kurt Hirschhorn (eds) Advances in hum genet. Plenum Press, New York, 22:117–152

Rossiter JP, Young M, Kimberland ML, Hutter P, Ketterling RP, Gitschier J, Horst J, et al (1994) Factor VIII gene inversions causing severe hemophilia A originate almost exclusively in male germ cells. Hum Mol Genet 3:1035–1039

Roth JR, Benson N, Galitski T, Haack K, Lawrence J, Miesel L. Rearrangements of the bacterial chromosome: formation and applications. In: Neidhardt FC (ed) *Escherichia coli* and *Salmonella typhimurium:* cellular and molecular biology. American Society for Microbiology, Washington, DC (in press)

Schmickel RD (1986) Contiguous gene syndromes: a component of recognizable syndromes. J Pediatr 109:231–241

Sonti RV, Roth JR (1989) Role of gene duplications in the adaption of *Salmonella typhimurium* to growth on limiting carbon sources. Genetics 123:19–28

Sturtevant AH (1924) The effects of unequal crossing over at the *Bar* locus in *Drosophila.* Genetics 10:117–147

Sutton E (1942) *Bar* eye in *Drosophila melanogaster:* a cytological analysis of some mutations and reverse mutations. Genetics 28:97–107

Tice SC (1914) A nev. sex-linked character in *Drosophila*. Biol Bull 26:221–230

Timmerman V, Nelis E, Van Hul W, Nieuwenhuijsen BW, Chen KL, Wang S, Ben Othman K, et al (1992) Peripheral myelin protein gene *PMP-22* is contained within the Charcot-Marie-Tooth disease type 1A duplication. Nat Genet 1:171–175

Tsubota SI (1991) Unequal crossing-over within the *B* duplication of *Drosophila melanogaster:* a molecular analysis. Genet Res Camb 57:105–111

Tsubota SI, Rosenbeg D, Szostak H, Rubin D, Schedl P (1989) The cloning of the *Bar* region and the *B* breakpoint in *Drosophila melanogaster:* evidence for a transposon-induced rearrangement. Genetics 122:881–890

Valentijn LJ, Baas F, Wolterman RA, Hoogendijk JE, van den Bosch NHA, Zorn I, Gabreels-Festen AAWM, et al (1992*a*) Identical point mutations of *PMP-22* in *Trembler*-J mouse and Charcot-Marie-Tooth disease type 1A. Nat Genet 2:288–291

Valentijn LJ, Baas F, Zorn I, Hensels GW, De Visser M, and Bolhuis PA (1993) Alternatively sized duplication in Charcot-Marie-Tooth disease type 1A. Hum Mol Genet 2:2143–2146

Valentijn LJ, Bolhuis PA, Zorn I, Hoogendijk JE, van den Bosch N, Hensels GW, Stanton VP, et al (1992*b*) The peripheral myelin gene *PMP-22/GAS-3* is duplicated in Charcot-Marie-Tooth disease type 1A. Nat Genet 1:166–170

Weinstock GM (1994) Bacterial genomes: mapping and stability. Am Soc Microbiol News 60:73–78

Wise CA, Garcia CA, Davis SN, Zhang H, Pentao L, Patel PI, Lupski JR (1993) Molecular analyses of unrelated Charcot-Marie-Tooth (CMT) disease patients suggest a high frequency of the CMT1A duplication. Am J Hum Genet 53:853–863