CRSQ CREATION RESEARCH SOCIETY QUARTERLY

Did Gene Duplication Produce Gene Families?

Yingguang Liu*

Abstract

Gene duplication is a process that produces extra copies of genes within the genome. Gene families are groups of similar genes, which evolutionist biologists believe to be products of gene duplication. In this paper, I argue that gene duplication is not the source of all of the modern gene families for the following reasons. (1) Most of the documented gene duplications are detrimental, and when beneficial, they cannot lead to new molecular functions. (2) Duplicated genes are usually silenced epigenetically, followed by degenerative mutations, ending up in non-functionalization. (3) Members of gene families are often components of irreducibly complex systems. (4) Regulation hierarchies, which have no counterparts in lower organisms, are required for proper expression of gene families. I propose the following criteria to distinguish between DNA sequences that were duplicated in history and paralogous genes that were created individually: First, copy-number polymorphisms among individuals of the same species obviously demonstrate recent duplications. Second, components of irreducibly complex systems are not likely products of gene duplications. These include genes with complex regulation hierarchies. Additional criteria are that the degree of sequence homology is a poor indictor to determine whether genes are duplicated, and the duplication by transposition is possible but is normally suppressed.

Introduction

Gene duplication is a specific type of "mutation" that increases the size of the genome. Major mechanisms of gene duplication include polyploidy, polysomy, unequal crossing-over, and transposition. The fate of duplicated genes, as well as the role of gene duplication in the history of life, has been a subject of much speculation and controversy. Most genes of "advanced" organisms have nonallelic homologues (paralogs) within the same genome, forming gene families. The degree of homology and functional similarities between paralogous genes vary from family to family. Are all gene families produced by ancient duplication events? If not, how can one distinguish between historical duplication and common design at the time of creation? This paper explores gene duplication in the light of genome-stabilizing mechanisms, as well as empirical findings about the function and regulation of well-known gene fami-

* Yingguang Liu, Maranatha Baptist Bible College, 745 W Main St., Watertown, WI 53094, Phone: 920-206-4045, E-mail: yliu@mbbc.edu

Accepted for publication April 15, 2008

lies, and argues that gene duplication followed by mutation cannot produce new molecular functions and therefore could not have produced paralogs with different functions. Although unequal crossing-over may alter the number of genes within a cluster of paralogs, I will show it is not accountable for the origin of the cluster.

Phenotypes of Gene Duplication

Duplication of large chromosomal segments or entire chromosomes causes severe imbalance between genes, resulting in malformation or diseases. Down's syndrome (trisomy 21 in human) is the best-known example. Even small duplications within protein-coding regions may cause problems such as frame-shift mutations (O'Dushlaine et al., 2005).

In polyploidy, however, all the genes of the genome are proportionally duplicated. Because polyploidy reduces the probability of homozygosity of inferior alleles, polyploid species may display increased vigor compared with their diploid parents. Furthermore, allopolyploidy can produce fertile hybrids in plants. However, it is noteworthy that the "new" phenotypes in polyploid species are all quantitative, not qualitative (Otto and Whitton, 2000). In other words, gene dosage effects may increase the biomass of the organism but does not produce new genetic products, only old ones produced in altered quantities. Even in allopolyploidy, the hybrid species merely demonstrate a combination of parental traits encoded by preexisting parental genes (Figure 1), just like allodiploids.

Polyploidy is rare in animals and most always lethal in birds, mammals, and human. Possible reasons include:

1. Chromosomal sex determination. "Advanced" animals are dioecious (having male reproductive organs in one individual and female in another), while most plants are not. Dioecy is typically determined by different combinations of sex chromosomes in male and female. In such animals, polyploidy leads to abnormal combinations of sex chromosomes, resulting in disturbed sexual development and sterility. However, this does not explain why most polyploid human and animals die as embryos.

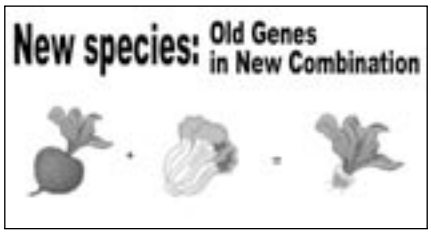


Figure 1. Allopolyploidy produces new species, but no new genes or new molecular functions. Raphanobrassica, a synthesis of radish (Raphanus) and cabbage (Brassica), has leaves of radish and roots of cabbage, therefore is inedible.

2. Genetic imprinting. In a diploid species, some genes from one parent are preferentially expressed in the early embryo. This is achieved by epigenetic modification of DNA during gametogenesis. Polyploidy will interfere with the expression of imprinted genes and therefore disturb embryonic development. Consistent with this theory, digynic (formed from diploid eggs) and dispermic (formed from fertilization by two sperm cells) human triploids demonstrate different survival time and pathological characteristics (Zaragoza et al., 2000). Plants have a haploid gametophyte phase in their life cycle and use different control mechanisms of imprinting than those of animals (Scott and Spielman, 2006).

3. Response to increased cell volume and decreased surface-to-volume ratio may be different in plants and animals, since plants have simpler body organization than animals.

Silencing and Degradation of Duplicated Genes

The cell is endowed with mechanisms to suppress duplicate genes (homology-dependent gene silencing) to prevent overexpression of gene products, such as RNAi, DNA methylation, and heterochromatin formation. The best-known example is inactivation of the extra X chromosome in human females. In plants, introducing extra copies of a gene often causes silencing of both the transgene and the endogenous gene (Flavell, 1994; Napoli et al., 1990). Similar phenomena are also found in other organisms, such as in fungi, drosophila, and mammals (Bhat, et al, 2004; Garrick et al., 1998). Gene silencing is especially prominent in polyploids (Adams et al., 2003).

Silencing of duplicated genes by cytosine methylation has been extensively studied. While methylation is reversible, methylated cytosine bases are prone to undergo spontaneous deamination and become thymines. C-T transition in CG-rich sequences, known as CG suppression, is especially common among duplicated genes (Lund et al., 2003) (Figure 2). Post-transcriptional gene silencing by double-stranded RNA is also employed by the cell to suppress duplicates (Agrawal et al., 2003; Saumet and Lecellier, 2006).

Figure 3 summarizes current theories about the fate of duplicated genes. Due to the lack of purifying selection, the fate for the vast majority of duplicates appears to be nonfunctional (pseudogenization). It is also possible that they could be subfunctional, but that leads to differentiation without innovation. Epigenetic complementation (EC theory, see Figure 3d) is the only mechanism whereby the duplicates may escape degenerative mutations, but the theory is inconsistent with the fact that most gene families are clustered and therefore in the same epigenetic environment. No mechanism for a neofunctional state has been proposed in these theories (Liu and Moran, 2006).

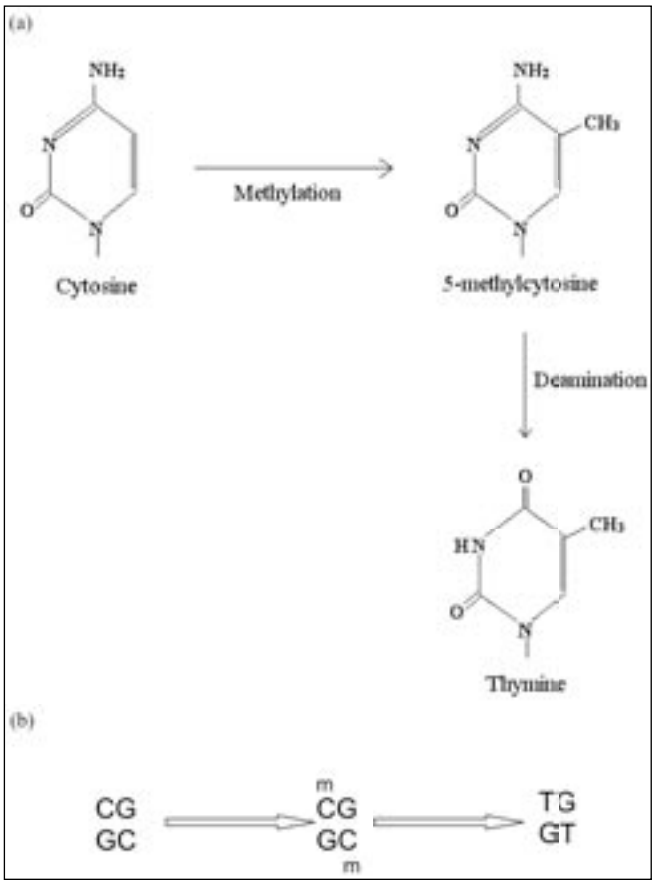


Figure 2. (a) Silencing by cytosine methylation. Spontaneous deamination of 5-methylcytosine may follow. (b) Transition of methylcytosine to thymine in CG islands inactivates a gene.

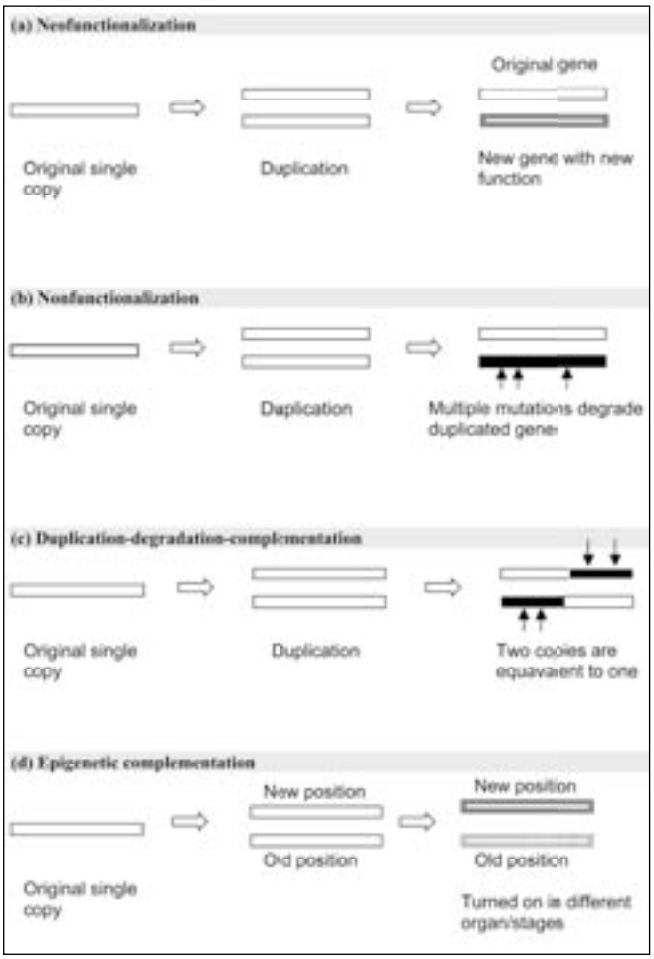


Figure 3. Proposed fates of duplicated genes. (a) Neofunctionalization of one copy while the other copy carries out the original function (Ohno, 1982; Taylor and Raes, 2004). (b) Nonfunctionalization of one copy due to accumulation of degenerative mutations (Lynch and Conery, 2000). (c) Partial degeneration of both copies may end up with two genes functioning as one (Force et al, 1999; Lynch and Force, 2000). (d) Duplicates function at different stages/ organs depending on position (Rodin et al, 2005; Rodin and Riggs, 2003).

Duplication and Gene Families

Of the known gene families, some have members that are structurally and functionally quite different, while others may consist of identical copies of the same gene. Many biologists assume that the degree of homology reflects the time available for random mutations after duplication and also assume without direct evidence that the genes are in fact duplicates. Below are proposed some rudimentary criteria to distinguish between historical duplications and gene families created in the beginning of life.

1. Irreducibly complex systems are not products of gene duplications. An irreducibly complex system is "a single system composed of several well-matched, interacting parts that contribute to the basic function, wherein the removal of any one of the parts causes the system to effectively cease functioning" (Behe, 1996, p. 39). Such a system cannot be built gradually by evolution. For example, several blood-clotting factors (factors II, VII, IX, and X) are homologous serine proteases. However, multiple duplication events must occur simultaneously, followed by coordinated creative mutations to produce a functional intermediate network from a proposed primitive clotting system (Davidson, et al, 2003; Liu and Moran, 2006). Some factors in

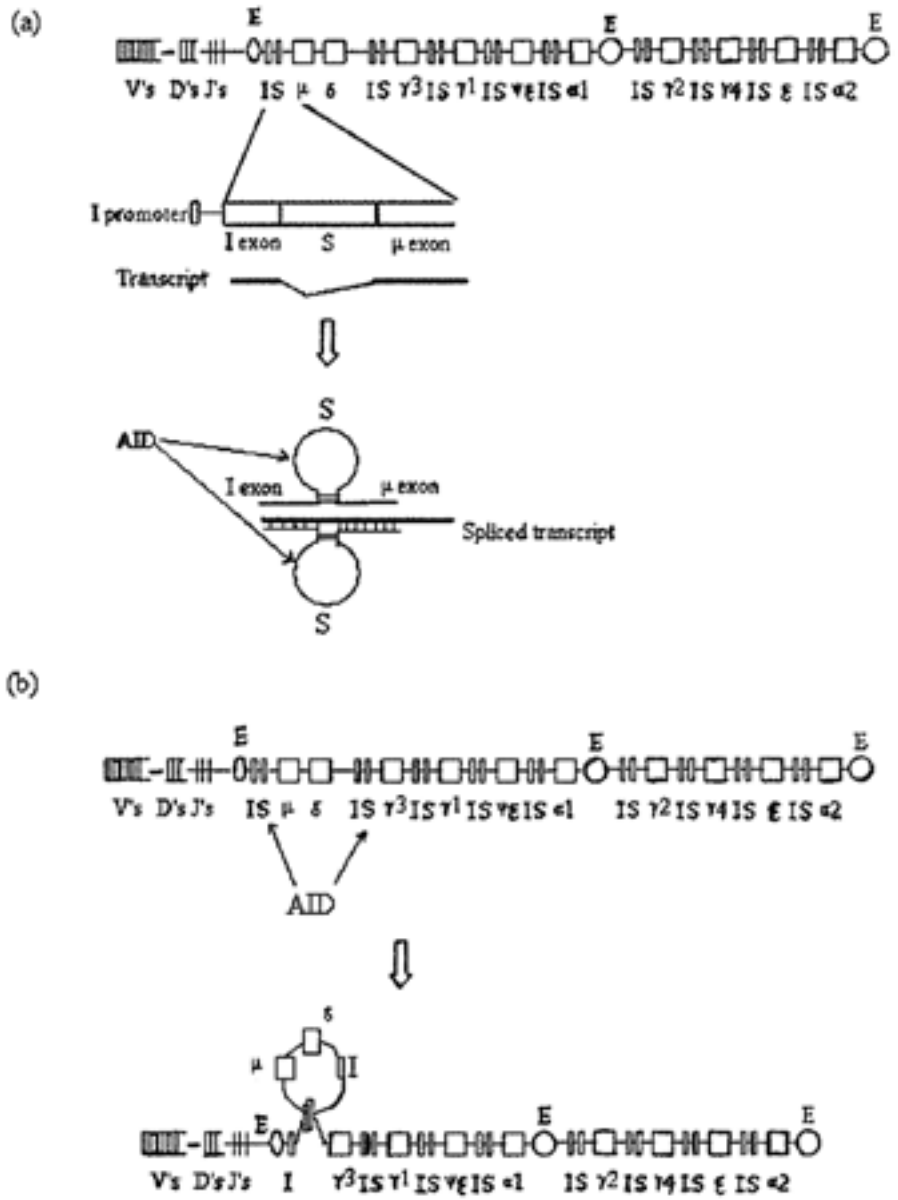


Figure 4. (a) Organization of the human immunoglobulin heavy chain constant locus. V, D, J: variable region genes; μ, δ, γ, ε, α: constant region genes; I: I promoter; S: switch region; E: enhancers. The region upstream of the μ heavy chain gene, including the I promoter, I exon, S region, as well as the 5' end of μ exon, is expanded to show an RNA transcript, which, after splicing, induces single-stranded loops in the S region. The loops, stabilized by both the transcript and stems formed from inverted repeats, are targets of the activation-induced deaminase (AID).

(b) AID recognizes the loops, deaminates cytosine, and in conjunction with uracil DNA glycolysase as well as an AP endonuclease, introduces double-stranded breaks in two S regions. The broken ends from different S regions are subsequently joined by the nonhomologous end-joining mechanism, eliminating the intervening sequences as a circle.

the system, such as factor V, do not have a preexisting paralog and therefore have to be created *de novo*.

2. Gene families with irreducibly complex regulation networks are not products of gene duplication. "Advanced" organisms have a significant fraction of their genomes as regulatory sequences, which have no homologues in simpler organisms (Liu and Doran, 2006). In systems, such as the immunoglobulin heavy chain genes, expression of the gene family is regulated with a unique set of cis and trans-acting factors that are not associated with the structural genes (Figure 4).

Expression of the constant region genes (μ, δ, γ, α, and ε) of immunoglobulin heavy chains is temporally regulated by a class-switch recombination mechanism illustrated in Figure 4. In humans and mammals, class switch requires simultaneous presence of two types of enhancers, the I promoters and S regions. Vertebrate animals lacking the S regions do not undergo class switching, even though they may possess linked heavy chain genes (Stavnezer and Amemiya, 2004). Deletion of any of these cis-elements in mice resulted in impaired class switching or no class switching (Cogne et al., 1994; Manis et al., 1998; Pinaud et al., 2001; Shinkura et al., 2003; Zhang et al., 1993).

The key enzyme, activation-induced deaminase (AID), is B-cell specific. Although it is also used in another process (somatic hypermutation of V regions), class switch requires a functional domain of the protein that is not needed for hypermutation (Barreto et al., 2003; Ta et al., 2003). There is strong evidence that other class-switch-specific enzymes/cofactors are required to guide μ—α, μ—γ, and μ—ε class switches (Ma et al., 2002; Ta et al., 2003).

Class switch also requires multiple enzymes involved in transcription, RNA splicing, excision repair, and nonhomologous end-joining (NHEJ) pathways. Although these enzymes are not class-

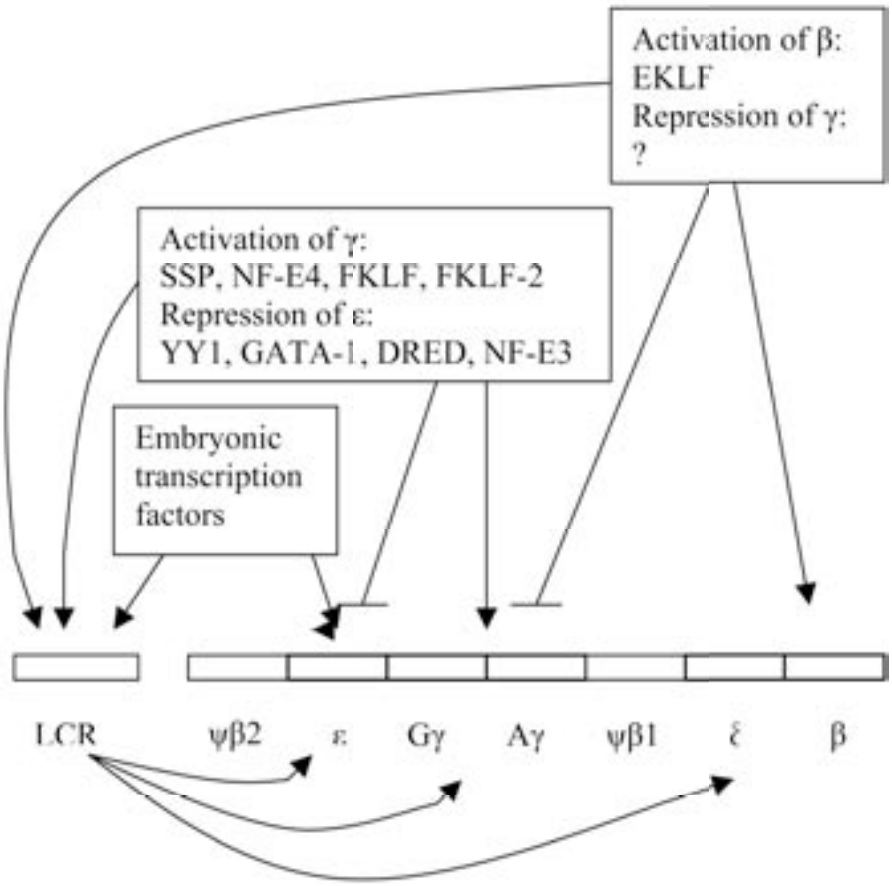


Figure 5. β-globin gene switching. Multiple erythroid-specific transcription factors act on the upstream locus control region (LCR) as well as the promoter of each gene to switch from embryonic (ε) to fetal (γ) then to adult (β and δ) globin types. -: repression; +: activation.

switch specific (and therefore could have evolved independently), their recruitment and coordination with the class-switch-specific factors necessitate careful design. For example, the spliced transcripts from I promoters are not translated, and their only known function is to initiate class switch. Production of these transcripts without simultaneous development of other factors for class switching would have been a mere waste of resources. Moreover, development of the class switching mechanism must be concomitant with differentiation of the various immunoglobulin isotypes (IgA, IgD, IgE, IgG, and IgM synthesized from the α, δ, ε, γ, and μ heavy chains, respectively). Switch without differentiation is futile, while differentiation without switch will fail to properly express these genes

More complicated than the immunoglobulin heavy chain gene family are members of the hemoglobin gene families. These genes are regulated both temporally and spatially. In the human β-gene family, ε is expressed in the yolk sac during the first six weeks of embryonic development, while the γ genes are expressed in the fetal liver, and β/δ genes are produced in the adult bone marrow. Different members of the family have different oxygen-binding functions suited for a particular developmental stage. Hemoglobin gene switching is less well understood than immunoglobulin class switching. Figure 5 delineates the factors discovered to date.

3. Degree of sequence homology is not a clear indicator of whether the genes are duplicates. In many cases, multiple identical copies of a gene are required for a normal cellular function, and therefore multiplicity must have been present from the beginning of the species. For example, multiple identical copies of ribosomal RNA genes (rDNA) are required for rapid production of ribosomes. In *E coli*, deletion of one or two of the seven copies of rRNA genes results in reduced growth rate and a prolonged lag phase (Stevenson and Schmidt, 2004). In *Drosophila*, reducing the number of rRNA genes causes bobbed mutants with decreased viability (Terracol and Prudhomme, 1986). Moreover, other genes are involved in maintaining multiplicity and organization of rRNA genes. In the yeast *Saccharomyces cerevisiae*, mutation of the Sgs1 gene causes reduction of rDNA copy number and accelerates aging of the cells (Sinclair and Guarente, 1997). The human homolog of Sgs1 is the WRN gene, mutation of which causes premature aging (Werner's syndrome) (Yu, et al., 1996). Indeed, cells from Werner's syndrome patients display more rearranged rRNA genes than normal cells (Caburet et al., 2005). Like in the yeast, loss of rRNA genes in human cells has been associated with aging (Zafiropoulos et al., 2005). Thus a certain degree of repetition of the rRNA genes appears to be essential for the viability of both prokaryotic and eukaryotic organisms. These genes appear to be created to function as a family, and organisms are endowed with other genes such as Sgs1 and WRN to maintain their copy numbers.

Because mutation invariably leads to diversification of repetitious genes, the cell must invoke some mechanisms, such as gene conversion, to maintain their homogeneity (Elder and Turner, 1995; Lewin, 2004; Polanco et al., 1998). The phenomenon is termed *concerted*

evolution by evolutionists, and the underlying mechanisms vaguely defined as "molecular drive" (Elder and Turner, 1995). Gene conversions must be biased toward one form to eliminate variations. These mechanisms only operate in certain gene families such as rRNA genes, but somehow restrained in other families such as human immunoglobulin V genes or MHC genes. It appears that some gene families are designed to be homogenous while others are designed to be diverse, and both must have existed as families from the beginning. Purifying selection keeps both categories from abnormal variations (Nei and Rooney, 2005).

4. Gene duplication causes copy number polymorphism within the same species or related species of a baramin. Clusters of homologous genes will predispose a chromosomal region to unequal crossing-over and thus cause variation in copy numbers. For example, due to the highly repetitive nature of the immunoglobulin heavy chain genes, this locus displays considerable polymorphism among the human population, depending on race. Duplications of the heavy chains genes are 22% in Mongoloids, 10% in Caucasians, and 5% in Negroids (Rabbani et al., 1996). These duplications cause no or slight elevation in serum immunoglobulin levels (Rabbani et al., 1995). Deletions are much rarer (1.5–3.5% depending on race), presumably due to negative selection.

The organization of the human immunoglobulin heavy chain gene family suggests that the segment from the I promoter of the γ3 gene to the first 3' enhancer may have been duplicated in history, producing the downstream γ2-γ4-ε-α2 cluster and an additional 3' enhancer. Subsequently, the upstream ε gene pseudogenized, while the downstream γ (2 and 4) genes subfunctionalized as evidenced by their inability to activate complements or to bind Fc receptors.

The clustered rRNA and histone genes also vary in number within species (Michel et al, 2005; Thomas et al., 2000), so are the clusters of human green visual pigment genes (Nathans et al., 1986a). Deletions of visual pigment genes due to unequal crossover may cause color blindness (Nathans et al., 1986b). With recent advances in genomics, copy-number polymorphism within species is receiving increasing attention (Sebat et al, 2004; Sharp et al., 2005).

5. Duplication by transposition is normally suppressed. Transposons are mobile DNA elements that can change locations (transpose) within the genome. While some transposons are excised from their original site and inserted into another site (cut-and-paste), others are duplicated onto a new site without losing the original copy (copy-and-paste). Most bacterial transposons are not transcribed during the transposition process, while most eukaryotic transposons are retrotransposons that involve an RNA intermediate for transposition. Transposition rearranges DNA and may serve as a means of regulating gene functions. Repeated copy-and-pasting is supposed to be accountable for the production of the abundant transposon families found in many creatures, especially human and mammals.

In reality, because transposition disrupts genes at the site of insertion, it is normally strictly controlled by the host cell and kept at low levels. Transposition in bacteria has an overall rate of $\sim 10^{-3}$–10^{-4} per element per generation. Retrotransposition of yeast *Ty* elements occurs at $\sim 10^{-7}$–10^{-8} (Lewin, 2004, pp. 470, 501). In *Drosophila*, failure to suppress transposition of the P element induces chromosomal breaks and causes sterility (hybrid dysgenesis). A variety of mechanisms have been discovered or proposed for silencing of transposons, including DNA methylation, RNA interference, interference of splicing, heterochromain formation, etc. (Agrawal et al, 2003; Cook and Karpen, 1994; Hashida et al, 2006; Lewin, 2004).

The vast majority of human transposons are not actively transposing. Insertion of transposons is responsible for only 0.1% of *de novo* mutations in human. However, in inbred mice, the percentage is more than 100 times higher and varies significantly between strains (Maksakova et al, 2006). Much of the discrepancy is due to the activity of a class of retrotransposon called endogenous retroviruses (ERVs). A minority of the mouse ERVs can actually produce infectious viral particles that efficiently infect the germ line (Lock et al, 1988). Not surprisingly, ERV insertions cause deleterious mutations, including carcinogenesis (Maksakova et al, 2006; Wang et al, 1997). The fact that some ERVs easily colonize the mouse genome and form gene families might be a consequence of the weakened immunity and compromised genome-stabilizing machinery due to inbreeding.

Interestingly, many human and vertebrate transposons are selectively transcribed in the germ line and in the embryo, suggesting a role of these elements in reproduction and development. Indeed, some transposons are found to encode proteins, called syncytins, essential for placental development (Dunlap et al, 2006). Others serve as regulating elements to drive tissue-specific expression of genes (see Bannert and Kurth, 2006 for review). Members of a transposon family may be regulated as a set during certain stage of development or under certain physiological situations. The human syncytin-1, encoded by an ERV, is regulated in part by an enhancer in the host sequence immediately upstream of the ERV (Prudhomme et al, 2004). The essentiality of the ERV and its collaboration with host elements suggest the ERV was designed and created *in situ* (Liu, 2006). These recent findings demonstrate that at least some transposons are not results of random transposition in history but were created

individually. At this point, we cannot rule out the possibility of generating nonessential members of transposon families by transposition.

Summary

Gene duplication is not a major means of innovation, as many contend. Duplicated genes are normally silenced and subjected to degenerative mutations. Gene families in modern genomes, at least some of them, were not created by gene duplication, although duplication may cause variations in family size. Furthermore, most gene regulation hierarchies are unique among "advanced" organisms and could not have been produced by duplication of primitive genes.

In-depth studies of copy-number polymorphisms within species will certainly shed more light on this topic. Observation of any new molecular functions in individuals with extra copies of a gene will nullify the above argument.

References

Adams, K.L., R.Cronn, R. Percifield, and J.F. Wendel. 2003. Genes duplicated by polyploidy show unequal contributions to the transcriptome and organ-specific reciprocal silencing. *Proceedings of the National Academy of Science, USA* 100:4649–4654.

Agrawal, N., P.V. Dasaradhi, A. Mohmmed, P. Malhotra, R.K. Bhatnagar, and S.K. Mukherjee. 2003. RNA interference: biology, mechanism, and applications. *Microbiology and Molecular Biology Reviews* 67:657–685.

Bannert, N., and R. Kurth. 2004. Retroelements and the human genome: New perspectives on an old relation. *Proceedings of the National Academy of Sciences, USA* 101(suppl 2):14572–14579.

Barreto, V., B. Reina-San-Martin, A.R. Ramiro, K.M. McBride, and M.C. 2003. Nussenzweig. C-terminal deletion of AID uncouples class switch recombination from somatic hypermutation and gene conversion. *Molecular Cell* 12:501–508.

Behe, M.J. 1996. *Darwin's Black Box*. The Free Press, New York, NY.

Bhat, A., R. Tamuli, and D.P. Kasbekar. 2004. Genetic transformation of Neurospora tetrasperma, demonstration of repeat-induced point mutation (RIP) in self-crosses and a screen for recessive RIP-defective mutants. *Genetics* 167:1155–1164.

Caburet, S., C. Chiara, S. Schurra, R. Lebofsky, S. J. Edelstein, and A. Bensimon. 2005. Human ribosomal RNA gene array display a broad range of palindromic structures. *Genome Research* 15:1079–1085.

Cogne, M., R. Lansford, A. Bottaro, J. Zhang, J. Gorman, F. Young, H.L. Cheng, and F.W. Alt. 1994. A class switch control region at the 3' end of the immunoglobulin heavy chain locus. *Cell* 77:737–747.

Cook, K.R., and G.H. Karpen. 1994. A rosy future for heterochromatin. *Proceedings of the National Academy of Science, USA* 91:5219–5221.

Davidson, C.J., E.G. Tuddenham, and J.H. McVey. 2003. 450 million years of hemostasis. *Journal of Thrombosis and Haemostasis* 1:1487–1494.

Dunlap, K.A., M. Palmarini, M.Varela, R.C. Burghardt, K. Hayashi, J.K. Farmer, and T.E. Spencer. 2006. Endogenous retroviruses regulate periimplantation placental growth and differentiation. *Proceedings of the National Academy of Science, USA* 103:14390–14395.

Elder, J.F. Jr., and B.J. Turner. 1995. Concerted evolution of repetitious DNA sequences in eukaryotes. *Quarterly Review of Biology* 70:297–320.

Flavell, R.B. 1994. Inactivation of gene expression in plants as a consequence of specific sequence duplication. *Proceedings of the National Academy of Science, USA* 91:3490–3496.

Force, A., M. Lynch, F.B. Pickett, A. Amores, Y.L. Yan, and J. Postlewait. 1999. Preservation of duplicate genes by complementary, degenerative mutations. *Genetics* 151:1531–1545.

Garrick, D., S. Fiering, D.I. Martin, and E. Whitelaw. 1998. Repeat-induced gene silencing in mammals. *Nature Genetics* 18:56–59.

Hashida, S.N., T. Uchiyama, C. Martin, Y. Kishima, Y. Sano, T. Mikami. 2006. The temperature-dependent change in methylation of the Antirrhinum transposon Tam3 is controlled by the activity of its transposase. *Plant Cell* 18:104–118.

Lewin B. 2004. *Genes VIII*. Pearson Education, Inc., Upper Saddle River, NJ.

Liu, Y. 2006. Were retroviruses created good? *JOBSS* http://www.answersingenesis.org/articles/am/v1/n2/were-retroviruses-created-good

Liu, Y., and D. Moran. 2006. Do new functions arise by gene duplication? *Journal of Creation* 20:82–89.

Lock, L.F., E. Keshet, D.J. Gilbert, N.A. Jenkins, and N.G. Copeland. 1988. Studies of the mechanism of spontaneous germline ecotropic provirus acquisition in mice. *The EMBO Journal* 7:4169–4177.

Lund, G., M. Lauria, P. Guldberg, and S. Zaina. 2003. Duplication-dependent CG suppression of the seed storage protein genes of maize. *Genetics* 165:835–848.

Lynch, M., and J.S. Conery. 2000. The evolutionary fate and consequences of duplicate genes. *Science* 290:1151–1155.

Lynch, M., and A. Force. 2000. The probability of duplicate gene preservation by subfunctionalization. *Genetics* 154:459–473.

Ma, L., H.H. Wortis, and A.L. Kenter. 2002. Two new isotype-specific switching activities detected for Ig class switching. *Journal of Immunology* 168:2835–2846

Maksakova, I.A., M.T. Romanish, L. Gagnier, C.A. Dunn, L.N. van de Lagemaat, D.L. Mager. 2006. Retroviral elements and their host: insertional mutagenesis in the mouse germ line. *PLoS Genetics* 2(1):e2.

Manis, J.P., N. van der Stoep, M. Tian, R. Ferrini, L. Davidson, A. Bottaro, and

F.W. Alt. 1998. Class switching in B cells lacking 3' immunoglobulin heavy chain enhancers. *Journal of Experimental Medicine* 188:1421–1431.

Michel, A.H., B. Kornmann, K. Dubrana, and D. Shore. 2005. Spontaneous rDNA copy number variation modulates Sir2 levels and epigenetic gene silencing. *Genes and Development* 19:1199–1210.

Napoli, C., C. Lemieux, and R. Jorgensen. 1990. Introduction of a chimeric chalcone synthase gene into petunia results in reversible co-suppression of homologous genes in trans. *Plant Cell* 2:279–289.

Nathans, J., D. Thomas, and D.S. Hogness. 1986a. Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. *Science* 232:193–202.

Nathans, J., T.P. Piantanida, R.L. Eddy, T.B. Shows, and D.S. Hogness. 1986b. Molecular genetics of inherited variation in human color vision. *Science* 232:203–210.

Nei, M., and A. P. Rooney. 2005. Concerted and birth-and-death evolution of multigene families. *Annual Review of Genetics* 39:121–152.

O'Dushlaine, C.T, R.J. Edwards, S.D. Park, and D.C. Shields. 2005. Tandem repeat copy-number variation in protein-coding regions of human genes. *Genome Biology* 6(8):R69.

Ohno, S. 1982. Evolution is condemned to rely upon variations of the same theme: the one ancestral sequence for genes and spacers. *Perspectives in Biology and Medicine* 25:559–572.

Otto, S.P., and J. Whitton. 2000. Polyploid incidence and evolution. *Annual Review of Genetics* 34:401–37.

Peaston, A.E., A.V. Evsikon, J.H. Graber, W.N. de Vries, A.E. Holbrook, D. Solter, and B.B. Knowles. 2004. Retrotransposons regulate host genes in mouse oocytes and preimplantation embryos. *Developmental Cell* 7:597–606.

Pinaud, E., A.A. Khamlichi, C. Le Morvan, M. Drouet, V. Nalesso, M. Le Bert, and M.Cogne. 2001. Localization of the 3' IgH locus elements that effect long-distance regulation of class switch recombination. *Immunity* 15:187–99.

Polanco, C., A.I. Gonzalez, de la Fuente, and G.A. Dover. 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.

Prudhomme, S., G. Oriol, and F. Mallet. 2004. A retroviral promoter and a cellular enhancer define a bipartite element which controls env ERVWE1 placental expression. *Journal of Virology* 78:12157–12168.

Rabbani, H., N. Kondo, C.I. Smith, and L. Hammarstrom. 1995. The influence of gene deletions and duplications within the IGHC locus on serum immunoglobulin subclass levels. *Clinical Immunology and Immunopathology* 76(3 Pt 2):S214–8.

Rabbani, H., Q. Pan, N. Kondo, C.I. Smith, and L. Hammarstrom. 1996. Duplications and deletions of the human IGHC locus: evolutionary implications. *Immunogenetics* 45(2):136–141.

Rodin, S.N., D.V. Parkhomchuk, and A.D. Riggs. 2005. Epigenetic changes and repositioning determine the evolutionary fate of duplicated genes. *Biochemistry (Mosc)* 70:559–567.

Rodin, S.N., and A.D. Riggs. 2003. Epigenetic silencing may aid evolution by gene duplication. *Journal of Molecular Evolution* 56:718–729.

Saumet, A., and C.H. Lecellier. 2006. Antiviral RNA silencing: do we look like plants? *Retrovirology* 3:3.

Scott, R.J., and M Spielman. 2006. Genomic imprinting in plants and mammals: how life history constrains convergence. *Cytogenetic and Genome Research* 113(1–4):53–67.

Sebat, J., B. Lakshmi, J. Troge, J. Alexander, J. Young, P. Lundin, S. Maner, H. Massa, M. Walker, M. Chi, N. Navin, R. Lucito, J. Healy, J. Hicks, K. Ye, A. Reiner, T.C. Gilliam, B. Trask, N. Patterson, A. Zetterberg, and M. Wigler. 2004. Large-scale copy number polymorphism in the human genome. *Science* 305:525–528.

Sharp, A.J., D.P. Locke, S.D. McGrath, Z. Cheng, J.A. Bailey, R.U. Vallente, L.M. Pertz, R.A. Clark, S. Schwartz, R. Segraves, V.V. Oseroff, D.G. Albertson, D. Pinkel, and E.E. Eichler. 2005. Segmental duplications and copy-number variation in the human genome. *American Journal of Human Genetics* 77:78–88.

Shinkura, R., M. Tian, M. Smith, K. Chua, Y. Fujiwara, and F.W. Alt. 2003. The influence of transcriptional orientation on endogenous switch region function. *Nature Immunology* 4:435–441.

Sinclair, D.A., and L. Guarente. 1997. Extrachromosomal rDNA circles—a cause of aging in yeast. *Cell* 91:1033–1042.

Stavnezer, J., and C.T. Amemiya. 2004. Evolution of isotype switching. *Seminars in Immunology* 16:257–275.

Stevenson, B.S., and T.M. Schmidt. 2004. Life history implications of rRNA gene copy number in *Escherichia coli*. *Applied and Environmental Microbiology* 70:6670–6677.

Ta, V.T., H. Nagaoka, N. Catalan, A. Durandy, A. Fischer, K. Imai, S. Nonoyama, J. Tashiro, M. Ikegawa, S. Ito, K. Kinoshita, M. Muramatsu, and T. Honjo. 2003. AID mutant analyses indicate requirement for class-switch-specific cofactors. *Nature Immunology* 4:843–848.

Taylor, J.S., and Raes, J. 2004. Duplication and divergence: the evolution of new genes and old ideas. *Annual Review of Genetics* 38:615–643.

Terracol, R., and N. Prudhomme. 1986. Differential elimination of rDNA genes in bobbed mutants of *Drosophila melanogaster*. *Molecular and Cellular Biology* 1023–1031.

Thomas, M.C., M. Olivares, M. Escalante, C. Maranon, and M. Montilla. 2000. Plasticity of the histone H2A genes in a Brazilian and six Colombian strains of Trypanosoma cruzi. *Acta Tropica* 75(2):203–210.

Wang, X.Y., L.S. Steelman, and J.A. McCubrey. 1997. Abnormal activation of cytokine gene expression by intracisternal

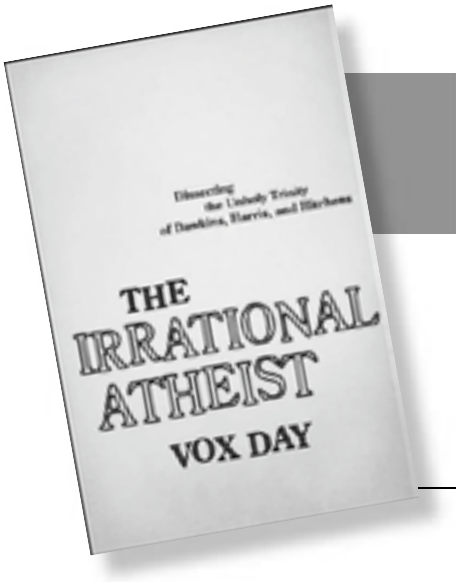
type A particle transposition: effects of mutations that result in autocrine growth stimulation and malignant transformation. *Cytokines, Cellular and Molecular Therapy* 3:3–19.

Yu, C.E., J. Oshima, Y.H. Fu, E.M. Wijsman, F. Hisama, R. Alisch, S. Matthews, J. Nakura, T. Miki, S. Ouais, G.M. Martin, J. Mulligan, and G.D. Schellenberg. 1996. Positional cloning of the Werner's syndrome gene. *Science* 272:258–262.

Zafiropoulos, A., E. Tsentelierou, M. Linardakis, A. Kafatos, and D.A. Spandidos. 2005. Preferential loss of 5S and 28S rDNA genes in human adipose tissue during ageing. *International Journal of Biochemistry and Cell Biology* 37:409–415.

Zaragoza, M.V., U. Surti, R.W. Redline, E. Milie, A. Chakravarti, and T.J. Hassold. 2000. Parental origin and phenotype of triploidy in spontaneous abortions: predominance of diandry and association with the partial hydatidiform mole. *American Journal of Human Genetics* 66:1807–1820.

Zhang, J., A. Bottaro, S. Li, V. Stewart, and F.W. Alt. 1993. A selective defect in IgG2b switching as a result of targeted mutation of the I gamma 2b promoter and exon. *The EMBO Journal* 12:3529-3537.



Book Review

The Irrational Atheist

by Vox Day

Ben Bella Books, Dallas, 2008, 305 pages, $25.00.

"The idea that he is a devotee of reason seeing through the outdated superstitions believed by less intelligent beings is the foremost conceit of the atheist" (p. 7). So starts Vox Day's demolition job on the various publications of the "New Atheists" in recent years. Perhaps it is a mark of a healthier Christianity that the spate of these polemics has been met with a variety of theological responses (Keller, 2008). But one of the most intriguing and by far the most entertaining is the effort of the self-styled Christian libertarian blogger, Vox Day, a.k.a. Theodore Beale, entitled *The Irrational Atheist*. Aside from the irreverent humor (the book begins with the sentence, "I don't care if you go to hell"), it is distinct in its narrow approach. The author states early on:

> I'm not trying to convince you that God exists. I'm not trying to convince you to accept Jesus Christ as your Lord and Savior. I'm not even trying to convince you that religious people aren't lunatics with low IQs who should be regarded with pity and contempt. But I am confident that I will convince you that this trio of New Atheists, this Unholy Trinity, are a collection of faux-intellectual frauds utilizing pseudo-scientific sleight of hand in order to falsely claim that religious faith is inherently dangerous and has no place in the modern world. (p. 7).

And in that narrow goal of making monkeys out of the leading lights of contemporary atheism, Day wildly exceeds his stated expectations. He begins by distinguishing between "High Church" atheists—the average university professor fits the mold—and "Low Church" atheists, or those that live as if there is no God while not thinking much about it on the way. He professes some sympathy for the latter: "There are far worse creeds to live by than shrug and let live" (p. 23). He also quickly grasps the connection between atheism and contemporary science.

> But it is impossible to separate atheism from science, because scientific materialism has such an influence on atheistic thinking even in matters where science is not directly involved. For some atheists, such as Richard Dawkins, science played an important role in causing them to abandon their former faiths but