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Report

The X Chromosome and the Rate of Deleterious Mutations in Humans

Francesco Giannelli and Peter M. Green

Division of Medical & Molecular Genetics, Guy's, King's & St. Thomas' School of Medicine, London

Monosomy for the X chromosome in humans creates a genetic Achilles' heel for nature to deal with. We report that the human X chromosome appears to have one-third the density of the coding sequence of the autosomes and, because of partial shielding from the high mutation rate of the male sex, that it should also have a lower mutation rate than the autosomes (i.e., .73). Hence, the X chromosome should contribute one quarter (.33 × .73 = .24) of the deleterious mutations expected from its DNA content. In this way, selection has possibly moderated risks from mutation in X-linked genes that are thought to have been fixed in their syntenic state since the onset of the mammalian lineage. The unexpected difference in the density of coding sequences indicates that our recent, hemophilia B–based estimate of the rate of deleterious mutations per zygote should be increased from 1.3 to 4 (1.3 × 3).

Intuitively, the rate of mutations per genome seems likely to be determined by a trade-off between the benefits of reducing the deleterious mutation rate and the cost of increasing fidelity.

The mammalian X chromosome could make an excessive contribution to the yield of deleterious mutations because of monosomy in males. Hence, McVean and Hurst (1997) proposed that selection would favor a lower mutation rate on the X chromosome and presented supporting data from mouse- and rat-sequence divergence. In birds, however, results were obtained that were inconsistent with this hypothesis (Ellegren and Fridolfsson 1997).

The idea of chromosome-specific mutation rates is not very attractive, because DNA sequence fidelity relies on general properties of replication, damage repair, and cellular checkpoints that monitor the integrity and successful replication of DNA during mitotic or meiotic cell cycles.

Nature could moderate the X-chromosome yield of deleterious mutations in other ways—for example, by ensuring that this chromosome has a small target for deleterious mutations per megabase of DNA. Chromosomal gene content does not seem strictly proportional to size, since (1) the phenotypic effects of trisomies are not a simple function of chromosome length (Jacobs and Hassold 1995); (2) dramatic interspecies differences exist in genome size (e.g., 3×10^9 bp in humans and 4×10^8 bp in *Fugu* [Brenner et al. 1993]), relative to gene number; (3) chromosomes vary in the content of DNA isochores associated with gene richness (Bernardi 1989); and (4) chromosome paint for CpG islands, which mark ~60% of genes (Antequera and Bird 1993), suggests a deficit in the human X chromosome (Craig and Bickmore 1994). These considerations prompted us to ask whether, on average, human X-linked genes show a smaller (than autosomal) ratio of coding to noncoding DNA.

We searched databases (GenBank and Integrated X Chromosome Database) for human X-linked genes with at least one autosomal homologue and known genomic and mRNA structure. Only groups of genes with identity $\geqslant$35% throughout the length of encoded proteins were considered.

Table 1 shows that a majority of X-linked genes are larger than their autosomal homologues, despite similar exon numbers. Some genes show similar base composition, and others show different levels of G+C richness. A+T-rich genes are usually larger than their G+C-rich homologues. On average, the X-linked genes available for comparison are threefold larger than their autosomal

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Address for correspondence and reprints: Prof. Francesco Giannelli, Division of Medical & Molecular Genetics, Guy's, King's & St. Thomas' School of Medicine, 8th floor, Guy's Hospital Tower, London Bridge, London SE1 9RT, United Kingdom. E-mail: francesco.giannelli@kcl.ac.uk

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Table 1

Structure of X-Linked Genes and Their Autosomal Homologues

X-Linked Gene					Autosomal Homologue				
Name	No. of Exons	mRNA (kb)	Size (kb)	Genomic G+C/ mRNA G+C (%)	Name	No. of Exons	mRNA (kb)	Size (kb)	Genomic G+C/ mRNA G+C (%)
AVPR	3	1.6	2	65/65	OXYR	4	4.1	18.9	?/49
GUCY	20	3.7	109	40/47	GUCY2D	20	3.6	12.8	61/65
PDK3	10	1.6	40	40/43	PDK4	11	1.8	10.6	36/46
PLS3	16	1.7	~90	?/42	LCP1	16	1.9	~90	?/46
F9	8	2.8	34	39/39	F10	8	2.5	~25	?/59
					F7	8	2.5	12	61/59
					PRTC	8	1.8	9	58/60
F8C	26	9	196	?/42	F5	25	6.7	~72	?/45
COL4A5	51	6.7	250	36/50	COL4A1	52	5	~100	?/60
COL4A6	46	6.4	~425	?/56					
DMD	79	14	~2,400	?/42	UTRN	?	13	~900	?/45
SLC6	13	3.7	8.6	65/62	SLC6A11	16	2	~25	?/56
					SLC6A2	14	1.9	45	?/57
TBG	5	1.8	5.2	41/43	P14	4	1.3	6.1	48/53
TIMP1	5	.8	~3	?/58	TIMP2	5	1	~83	?/65
					TIMP3	5	4.6	61	?/49
Average		4.48	296.9				3.58	98.0	

homologues. There are still few informative genes, but the X-chromosome and autosomal sequences available provide further data.

The sequence of chromosome 22 was announced recently (Dunham et al. 1999), and much of the X chromosome has been sequenced. Using AceBrowser, we examined the 22.7 Mb of chromosome 22 and the 39.8 Mb of the X chromosome, sequenced and annotated using identical criteria at the Sanger Centre. This showed 752 and 1,405 exons (pseudogenes and noncoding exons were excluded) in the X-chromosome and chromosome 22 sequences (table 2). The latter showed 2.55 times more coding information per megabase than the former, in keeping with the data on the aforementioned X-linked and homologous autosomal genes. Hence, the X chromosome appears to have a lower gene density and should yield fewer deleterious mutations per megabase of DNA. This contrasts with the suggestion by Cooper and Schimtke (1984), who noted a lower level of RFLP heterozygosity on the X chromosome, relative to the autosomes, and who suggested that this might be explained by the X chromosome being particularly rich in coding and regulatory sequences.

The sequence variation observed by the authors of these earlier reports is expected to be essentially neutral, and a better explanation for the low level of "neutral" sequence variations on the X chromosome arises from consideration of the joint consequences of the two following facts. There are only three X chromosomes, versus four of each type of autosome, so that a site on the X chromosome has three fourths the chance of mutating of a site on an autosome. The X chromosome spends only one-third of its time in males, versus half for the autosomes. Therefore, the overall mutation rate of the X chromosome should be lower than that of the autosomes, when the male:female ratio of mutation rates is >1. Using data from the U.K. hemophilia B population, we have directly estimated (Green et al. 1999) that this ratio is 8.6, and, consequently, the human X-chromosome mutation rate should be 27% lower than that of autosomes $\{[1 - (2 + 8.6) \times 2/(1 + 8.6) \times 3] \times 100 = 27\}$. In addition, background selection against recessive deleterious mutatins will further reduce the frequency of neutral variation on the X chromosome relative to autosomes (Charlesworth 1994).

Ohno (1967) has presented compelling arguments to suggest that the development of an X-Y sex-chromosome dimorphism and the device of X inactivation to achieve dosage compensation have constrained the evolution of the X chromosome in the mammalian lineages, so that its gene composition, in contrast to that of individual autosomal pairs, has been conserved. It follows from this—now known as Ohno's law—that the

Table 2

Coding Sequence in X-Chromosome and Chromosome-22 Regions Examined at the Sanger Centre

	Chromosome		
	X	22	X:22 Ratio
Finished sequence (Mb)	39.8	22.7	1.75
No. of exons	752	1,405	.535
Sum of exon length (bp)	153,603	223,730	.686
Sequence ratio (total:exon)	259	101	2.55

X chromosome has not been able to escape the selective pressures mentioned at the outset of this report, by reducing or substantially changing its gene content during the evolution of the mammalian lineage.

The mammalian method of X-linked gene-dosage compensation results in the activity of only one X chromosome in female somatic cells from early embryonic life (Lyon 1998). It follows that, uniquely in mammals (Lucchesi 1998), even females are exposed to some risk from X-linked gene hemizygosity. This further increases the pressure of purifying selection. A small target for deleterious mutations in the X chromosome thus seems appropriate.

Lyon (1998) reviewed evidence on the spreading of X inactivation and proposed that this is favored by interspersed repetitive elements of the LINE (long interspersed repeat-sequence element) type that may have accumulated in the X chromosome under the influence of selection. Hence, a single process may have favored X inactivation and low target density for deleterious mutations.

In view of the lower density (.33) of coding sequences that we found on the X chromosome and the lower X-chromosome mutation rate resulting from the high male: female ratio of mutation rates (1 − .27 = .73), we propose that the rate of deleterious mutations per megabase of X chromosome should be only one quarter (.73 × .33 = .24) of that per autosomal megabase.

Recently, we suggested that a human zygote carries 128 new mutations, of which 1.3 are deleterious or, according to our definition, capable of causing clinically detectable effects in the hemizygous state (Giannelli et al. 1999). We based our calculations on data from X-linked hemophilia B but did not take into account the X chromosome's threefold-lower target density for deleterious mutations. Therefore, a value of four deleterious mutations (i.e., 1.3 × 3.3) per human zygote is more appropriate. Such a rate suggests that the continued existence of our species probably depends on quasi-truncating selection and recombination, to allow elimination of chromosomal regions carrying deleterious mutations (Kondrashov 1988; Crow 1997).

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Electronic-Database Information

URLs for data in this article are as follows:

AceBrowser, Chromosome 22, http://webace.sanger.ac.uk/cgi-bin/ace/simple/22ace

AceBrowser, Chromosome X, http://webace.sanger.ac.uk/cgi-bin/ace/simple/Xace

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/index.html

Integrated X Chromosome Database, http://ixdb.molgen.mpg.de

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