Hum Genet
DOI 10.1007/s00439-013-1291-6

LETTER TO THE EDITOR

At what rate do new premutation alleles arise at the fragile X locus?

Diane P. Genereux · Charles D. Laird

Received: 1 June 2012 / Accepted: 14 March 2013

Two mutation rates are the key to understanding the population dynamics of fragile X syndrome. Hagerman (2008) estimated one of these mutation rates from empirical data: the rate at which premutation alleles at the fragile X locus, *FMR1,* undergo further expansion to the full-mutation alleles that can give rise to fragile X syndrome. Here, we use newly published empirical data to estimate the other: the rate at which premutation alleles arise, de novo, in the United States population.

Before the molecular characterization of the *FMR1* locus, it seemed that almost all full-mutation fragile X alleles arose through further expansion of existing premutation alleles segregating in families (see, e.g. Smits et al. 1992), with no evidence that new premutation alleles could be produced through mutational expansion of smaller alleles. However, several mutation-selection balance models suggested that fragile X mutation rates would have to be quite high to explain the observed frequency of males with fragile X syndrome, especially given the reduced reproductive fitness of these individuals. Mutation rates estimated under these population-genetic models ranged from 0.00010 to 0.00072 (Table 1)—values at the high end of the range reported for disease-causing alleles at other human loci (Vogel and Motulsky 1986). Here, we use published data on *FMR1* allele frequencies and expansion probabilities to calculate the rate at which new *FMR1* premutation alleles arise in the United States. Our results are in accord with several earlier population-genetic estimates of a very high mutation rate for *FMR1*.

Existing data indicate that new premutation alleles arise mostly or exclusively via expansion of intermediate alleles, which are defined as having CGG-repeat numbers ranging from 45 to 54. In a study of more than 1,000 parent-to-child transmissions of normal alleles, which have fewer than 45 repeats, Nolin et al. (2011) reported no transitions directly into the premutation class. These empirical findings inform our approach of calculating the overall rate at which new premutation alleles arise, using exclusively mutation rate and frequency data for intermediate alleles.

Table 1 Estimates of the rate at which new premutation alleles arise, as inferred in published population-genetic models

Study	Estimate of rate of new premutations
Sherman et al. (1984)	*0.00072*
Sherman et al. (1985)	0.00024
Vogel et al. (1985)	0.00010
Winter (1987)	0.00017
Vogel et al. (1990)	0.00010
Sved and Laird (1990)	*0.00033*
Morton and Macpherson (1992)	0.00025
Kolehmainen (1994)	*0.00038*
Morris et al. (1995)	0.00019
Ashley and Sherman (1995)	0.00025

Estimates highlighted in italics are within the 95 % confidence interval we calculate here from empirical data (see Table 2). The estimate from Sherman et al. (1984) is specific to mutations occurring in the male germ line. Values given for Vogel et al. (1990) and Ashley and Sherman (1995) are at the upper ends of their respective intervals

D. P. Genereux (✉)
Department of Biology, Westfield State University,
577 Western Avenue, Box 1630, Westfield,
MA 01086-1630, USA
e-mail: dgenereux@westfield.ma.edu

C. D. Laird
Department of Biology and Center on Human Development and Disability, University of Washington, Seattle, WA 98195, USA

Published online: 07 April 2013

Table 2 Inference of de novo premutation rate from published data on intermediate-allele frequencies and mutation rates

Intermediate-allele size class	Study	45 to 49 repeats				50 to 54 repeats			
		Observed	Total	Overall estimate	95 % CI	Observed	Total	Overall estimate	95 % CI
Alleles in size class out of total alleles sampled	Cronister et al. (2008)	134	9721	0.0137	(0.011, 0.016)	49	9721	0.005	(0.0036, 0.0064)
Premutations arising from alleles of this size class	Cronister et al. (2008)	1	40			3	20		
	Nolin et al. (2011)	0	55	0.0105	(0, 0.023)	5	51	0.113	(0.09, 0.134)
Frequency-weighted de novo premutation rate for size class				0.000144	(0, 0.00037)			0.00057	(0.000349, 0.00086)
Overall estimated de novo premutation rate								0.00071	(0.00031, 0.0012)

To estimate the overall rate at which premutation alleles arise de novo, we compiled information from Cronister et al. (2008) and from Nolin et al. (2011). These studies reported transition rates for two subsets of intermediate alleles: those with 45 to 49 CGG repeats and those with 50 to 54 CGG repeats (Table 2). We weighted these reported transition rates using information on the frequencies of alleles in these two subsets (Cronister et al. 2008; A. Cronister, personal communication), yielding a weighted mean rate of 0.00071 new premutation alleles per conception, with a broad confidence interval (95 % CI 0.00031, 0.0012; Table 2).

The confidence interval on our estimate of the rate of de novo premutation events spans some of the mutation rate estimates made previously using mathematical models (in italics on Table 1: Sherman et al. 1984; Sved and Laird 1990; Kolehmainen 1994), but is somewhat higher than the values inferred under others of those models (Table 1: Sherman et al. 1985; Vogel et al. 1985; Winter 1987; Vogel et al. 1990; Morton and Macpherson 1992; Morris et al. 1995; Ashley and Sherman 1995). Overall, however, all of these early population-genetic models were consistent in predicting a high mutation rate either close to or within the confidence interval on the value we calculate here from published empirical data (Table 1).

Our present study estimates the rate at which premutation alleles are produced, de novo, in the US population. Variation in patterns of AGG interspersion and in other haplotype features has been found to modulate the stability of the CGG-repeat region (Eichler et al. 1994, 1995; Curlis et al. 2005). Global variation in the frequencies of these haplotypes thus could yield substantial variation in the rate of such de novo events, as first suggested by Richards et al. (1992) and Jacobs et al. (1993). To further investigate these possibilities, it will be necessary to collect allele-frequency and transition-rate data from populations around the world. In populations where premutation alleles are very rare (e.g. Otsuka et al. 2010), it is likely that only very large data sets will reveal mutation events that gave rise to new premutation alleles. Data on allele frequencies and transition rates for individual populations will be of clinical value, as it is increasingly clear that individuals with *FMR1* premutations are at risk of a broad range of clinically relevant phenotypes, including FXTAS and FXPOI (Cronister et al. 1991; Chonchaiya et al. 2009).

Acknowledgments We are grateful to Amy Cronister for sharing additional data on the size distribution of the intermediate alleles initially reported in Cronister et al. (2008). This research was supported by National Institutes of Health (NIH) grants HD002274 and GM077464. DPG was supported in part by the Jaconnette L. Tietze Young Scientist Award.

References

Ashley AE, Sherman SL (1995) Population dynamics of a meiotic/mitotic expansion model for the fragile X syndrome. Am J Hum Genet 57:1414–1425

Chonchaiya W, Schneider A, Hagerman RJ (2009) Fragile X: a family of disorders. Adv Pediatr 56:165–186

Cronister A, Schreiner R, Wittenberger M, Amiri K, Harris K, Hagerman RJ (1991) Heterozygous fragile X female: historical, physical, cognitive, and cytogenetic features. Am J Med Genet 38:269–274

Cronister A, Teicher J, Rohlfs EM, Donnenfeld A, Hallam S (2008) Prevalence and instability of fragile X alleles: implications for offering fragile X prenatal diagnosis. Obstet Gynecol 111:596–601

Curlis Y, Zhang C, Holden JJA, Loesch PKKD, Mitchell RJ (2005) Haplotype study of intermediate-length alleles at the fragile X (FMR1) gene: ATL1, FMRb, and microsatellite haplotypes differ from those found in common-size FMR1 alleles. Hum Biol 77:137–151

Eichler EE, Holden JJA, Popvich BW, Reiss AL, Snow K, Thibodeau SN, Richards CS, Ward PA, Nelson DL (1994) Length of

uninterrupted CGG repeats determines the instability of the *FMR1* gene. Nat Genet 8:88–94

Eichler EE, Hammond HA, Macpherson JN, Ward PA, Nelson DL (1995) Population survey of the human FMR1 CGG repeat substructure suggests biased polarity for the loss of AGG interruptions. Hum Mol Genet 4:2199–2208

Hagerman PJ (2008) The fragile X prevalence paradox. J Med Genet 45:498–499

Jacobs PA, Bullman H, Macpherson J, Youings S, Rooney V, Watson A, Dennis NR (1993) Population studies of the fragile X: a molecular approach. J Med Genet 30:454–459

Kolehmainen K (1994) Population genetics of fragile X: a multiple allele model with variable risk of CGG repeat expansion. Am J Med Genet 51:428–435. doi:10.1002/ajmg.1320510425

Morris A, Morton NE, Collins A, Lawrence S, Macpherson JN (1995) Evolutionary dynamics of the FMR1 locus. Ann Hum Genet 59:283–289

Morton NE, Macpherson JN (1992) Population genetics of the fragile-X syndrome: multiallelic model for the FMR1 locus. Proc Natl Acad Sci USA 89:4215–4217

Nolin SL, Glicksman A, Ding X, Ersalesi N, Brown WT, Sherman SL, Dobkin C (2011) Fragile X analysis of 1112 prenatal samples from 1991 to 2010. Prenat Diagn 31:925–931

Otsuka S, Sakamoto Y, Siomi H, Itakura M, Yamamoto K, Matumoto H, Sasaki T, Kato N, Nanba E (2010) Fragile X carrier screening and *FMR1* allele distribution in the Japanese population. Brain Dev 32:110–114

Richards RI, Holman K, Friend K, Kremer E, Hillen D, Staples A, Brown WT et al (1992) Evidence of founder chromosomes in fragile X syndrome. Nat Genet 1(4):257–260. doi:10.1038/ng0792-257

Sherman SL, Morton NE, Jacobs PA, Turner G (1984) The marker (X) syndrome: a cytogenetic and genetic analysis. Ann Hum Genet 48:21–37

Sherman SL, Jacobs PA, Morton NE, Froster-Iskenius U, Howard-Peebles PN, Nielsen KB, Partington MW et al (1985) Further segregation analysis of the fragile X syndrome with special reference to transmitting males. Hum Genet 69:289–299

Smits A, Smeets D, Hamel B, Dreesen J, van Oost B (1992) High prevalence of the fra(X) syndrome cannot be explained by a high mutation rate. Am J Med Genet 43:345–352

Sved JA, Laird CD (1990) Population genetic consequences of the fragile-X syndrome, based on the X-inactivation imprinting model. Am J Hum Genet 46:443–451

Vogel F, Motulsky AG (1986) Human Genetics, Vol 2. Springer, Berlin

Vogel F, Krüger J, Brøndum Nielsen K, Fryns JP, Schindler D, Schinzel A, Schmidt A, Schwinger E (1985) Recurrent mutation pressure does not explain the prevalence of the marker X syndrome. Hum Genet 71:1–6

Vogel F, Crusio WE, Kovac C, Fryns JP, Freund M (1990) Selective advantage of fra (X) heterozygotes. Hum Genet 86:25–32

Winter RM (1987) Population genetics implications of the premutation hypothesis for the generation of the fragile X mental retardation gene. Hum Genet 75:269–271