Genetic Variation Versus Recombination Rate in a Structured Population of Mice

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The correlation between genetic variation and recombination rate was investigated in a structured mouse population. Nucleotide sequence data from 19 autosomal DNA loci from eight inbred strains of mouse (*Mus musculus*) sampled from three major subspecies were analyzed. The recombination rate was estimated from the comparison of genetic and physical map distances between markers flanking a 10-cM region of each locus. The strains were categorized into four groups (subpopulations) based on geography. By partitioning the genetic diversity into within-group and among-group variation, we detected a positive correlation between the recombination rate and nucleotide diversity within groups. The level of nucleotide differentiation among groups (G_{ST}) showed a negative correlation with the rate of recombination. There was no significant correlation between recombination rate and nucleotide diversity when data from different subpopulations were pooled. No correlation was detected between recombination rate and nucleotide divergence of *M. musculus* and *M. spicilegus*. These patterns deviate from the strict neutral expectation under the constant nucleotide substitution rate, and they are likely to have been formed either by a hitchhiking effect of positively selected mutants or by background selection of deleterious mutants occurring in a subdivided population. Our series of comparisons show that because a real population always has some structure, incorporation of its information is important in detecting non-neutral evolution.

Introduction

Detecting the effect of natural selection in a structured population has thus far been a challenge. A number of methods have been proposed for detection of natural selection in a ''panmictic population.'' One of the most commonly used approaches is to investigate whether the frequency spectrum of silent polymorphic sites deviates from the neutral expectation (Tajima 1989; Fu and Li 1993). An excess of high-frequency–derived variants may be the strongest evidence for positive selection (Fay and Wu 2000). However, this approach may be problematic; a real population usually has some structure, and unequal sampling from a structured population can result in a spurious Fay and Wu test (Przeworski 2002). Thus, ignoring the population structure is likely to obscure any pattern of selection, and this approach requires caution when the neutral model is being tested (e.g., Wall 1999).

The effect of natural selection in a panmictic population can also be inferred from the presence of a positive correlation between recombination rate and nucleotide diversity. This correlation has been observed in *Drosophila* (Begun and Aquadro 1992; Aquadro, Begun, and Kindahl 1994; Andolfatto and Przeworski 2001), human (Nachman et al. 1998; Przeworski, Hudson, and Di Rienzo 2000; Nachman 2001, Lercher and Hurst 2002), and mouse (Nachman 1997). The pattern has been explained mainly by the genetic hitchhiking of rapidly fixed advantageous mutations (Maynard Smith and Haigh 1974; Kaplan, Hudson, and Langley 1989) and/or by background selection against deleterious mutations (Charlesworth, Morgan, and Charlesworth 1993; Charlesworth, Charlesworth, and Morgan 1995; Hudson and Kaplan 1995). The hitchhiking hypothesis has been supported well by empirical data in *Drosophila* (e.g., Aquadro, Begun, and Kindahl 1994; Langley et al. 2000; Andolfatto and Przeworski 2001). However, in a pooled sample of a subdivided population, the correlation is likely to become weak if the pattern of natural selection varies among subpopulations. In this case, population structure has to be taken into account. For example, a subdivided population model of genetic hitchhiking is proposed by Slatkin and Wiehe (1998). They showed that under some conditions, hitchhiking can lead to substantial population differentiation, as measured by Wright's F_{ST}. They also suggested that if subpopulations were completely isolated, greater differentiation would be found in regions of a genome with a lower rate of recombination. Thus, in their model, genetic hitchhiking is likely to form a negative correlation between recombination rate and population divergence.

There are a few observations in *Drosophila* supporting a negative correlation between F_{ST} and the rate of recombination. For example, Stephan and Mitchell (1992) found reduced variation within populations and increased divergence between populations of *Drosophila ananassae* in India and Burma in regions with reduced recombination on the X chromosome. Begun and Aquadro (1993) found elevated F_{ST} in three of seven genomic regions with a reduced recombination rate in populations of *Drosophila melanogaster* in Zimbabwe and other localities. Both of these studies invoked genetic hitchhiking events as the cause (see also Stephan 1994). Nevertheless, it should be noted that the background selection model also predicts increased F_{ST} values in regions of reduced recombination (Charlesworth, Nordborg, and Charlesworth 1997), and it is indistinguishable from the hitchhiking model in the absence of a rigorous quantitative study (e.g., Stephan et al. 1998).

In this study, we have analyzed the sequences of 21 nuclear genes in nine inbred mouse strains from three major subspecies of *Mus musculus*. (Liu, Takahashi,

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Key words: *Mus musculus*, recombination rate, population structure, population subdivision, genetic hitchhiking, background selection, F_{ST}.

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Mol. Biol. Evol. 21(2):404–409. 2004
DOI: 10.1093/molbev/msh030
Advance Access publication December 5, 2003
Molecular Biology and Evolution vol. 21 no. 2

Table 1
Mouse Strains Used in This Study

Species	Subspecies	Strain	Origin
Mus musculus	*domesticus*	Pgn2	Canada
		BFM/2	France
	musculus	BLG2	Bulgaria
		NJL	Denmark
	molossinus[a]	MSM	Japan
		SWN	Korea
	castaneus	CAST/Ei	Thailand
		HMI	Taiwan
Mus spicilegus (outgroup)		ZBN	Bulgaria

[a] Originated from the hybrids of *M. m. musculus* and *M. m. castaneus* (Yonekawa et al. 1988).

Kitano, Koide, Shiroishi, Moriwaki, and Saitou, unpublished data). This sequence data showed overall clustering of the strains within subspecies, with traces of genetic exchange between them, suggesting a large ancient population size and fairly vague subspecies level divergence in this species. Hence, these samples represent a structured population. To define closely related groups as units of a subpopulation in this species, we categorized the strains into four geographically related groups. Here, we investigate (1) whether the phenomenon of increased population divergence in regions of reduced recombination exists in mouse and (2) whether the effect of natural selection on linked neutral variation can explain the relationships between genetic variation and rate of recombination in this structured population.

Materials and Methods

Mouse Strains and Nucleotide Sequence Data

DNA sequences of 19 autosomal genes from eight inbred strains of *Mus musculus* and one strain of *Mus spicilegus* were analyzed. The mouse strains used in this study are listed in table 1. All the sequence data used in this study are available from the DDBJ/EMBL/GenBank Database. The accession numbers of these sequences are AB039045 through AB039223. The strains of *Mus musculus* were categorized into four closely related groups based on subpopulations found in this species (table 1). We categorized Pgn2 and BFM/2 as *M. m. domesticus* group, BLG2 and NJL as *M. m. musculus* group, CAST/Ei and HMI as *M. m. castaneus* group, and MSM and SWN as *M. m. molossinus* group. ZBN is an inbred strain of *M. spicilegus* used as an outgroup. All of these inbred strains are wild-caught and have been maintained at our National Institute of Genetics (details described in Koide et al. 2000). Two genes on the sex chromosomes also in the database were excluded from the analyses because they are assumed to have smaller N_es than the rest of the loci.

Recombination Rate Estimates

The rates of recombination across the mouse genome were estimated by comparing the genetic map and the high-density radiation hybrid (RH) map (physical map; Van Etten et al. 1999). The map distance data were taken from Whitehead Institute/MIT Center for Genome Research, Mouse EST RH Mapping Project, Public Data Release 10 (December 2001). The genetic map distance (cM) and the RH map distance (cR = centiRay) between the two markers flanking the ± 5 cM (10 cM) region of the locus were used to calculate the recombination rate (cM/cR). For each of the two loci, *Fau* and *Fut4*, whose genetic map positions are both 3.0 cM from the distal end of their chromosomes, a marker at the distal end of the chromosome and another marker flanking the proximal 10 cM region from it were used. The markers and their map positions used to calculate recombination rates are listed in table 2.

Estimation of Genetic Variation

The level of genetic variation is estimated based on pairwise sequence differences of synonymous sites and introns. The sequence data of the *Fut4* locus has suggested an introgression from other distant taxa in the BLG2 strain (Liu, Takahashi, Kitano, Koide, Shiroishi, Moriwaki, and Saitou, unpublished data); thus this strain is excluded from the analyses of this locus. Genetic variation within subpopulations (π within subpopulation) was calculated as the average number of pairwise nucleotide differences per site (nucleotide diversity; Nei 1987) between the sequences of the four (three for *Fut4*) pairs of strains from the same subpopulations (pairs of Pgn2-BFM/2 for subpopulation *domesticus*; BLG2-NJL, for *musculus*; CAST/Ei-HMI, for *castaneus*; and MSM-SWN, for *molossinus*). Genetic variation between subpopulations (d) is defined as the average number of pairwise nucleotide differences per site between the rest of the 24 (18 for *Fut4*) combinations of strains from different subpopulations. The relative level of population divergence was calculated as

$$G_{ST} = (\pi \text{ total} - \pi \text{ within subpopulation})/\pi \text{ total},$$

following Nei (1973). π total is the average number of pairwise nucleotide differences per site calculated from all 28 (21 for *Fut4*) combinations of the strains. Because π total of *Hoxa2* was 0, G_{ST} of this locus was not calculated.

Results and Discussion

The mouse strains used in our study are wild-caught inbred lines from different subspecies of *Mus musculus*. This species is normally classified into four authentic subspecies, *M. m. domesticus*, *M. m. musculus*, *M. m. castaneus*, and *M. m. bactrianus* (Bonhomme and Guenet 1989; Sage, Atchley, and Ernesto 1993). We sampled two strains each from the first three subspecies and two strains from *M. m. molossinus*, which is a local population (or a subspecies) known to have originated from hybrids of *M. m. musculus* and *M. m. castaneus* (Yonekawa et al. 1988; table 1). Our definition of these four groups as subpopulations reflects the structure of the whole species; however, migration rates cannot easily be determined. For example, the discovery of a narrow hybrid zone between *M. m. domesticus* and *M. m. musculus* suggests the existence of a reproductive barrier (reviewed in Sage, Atchley, and Ernesto 1993), although there is evidence

Table 2
Recombination Rate Estimates of the 19 Mouse Genes Analyzed in This Study

Gene Symbol	Chromosome: Genetic Map Position (cM)[a]	Markers[b]: Genetic Map Position (cM)	Recombination Rate (cM/cR)[c]	Recombination Rate (10^{-1} × cM/Mb)[d]
B3galt1 (b3GT1)	**2:** 38[e]	D2Mit324 (32.8) D2Mit245 (43.7)	0.058	0.088
B3galt2 (b3GT2)	**1:** 78[e]	D1Mit193 (71.0) D1Mit107 (83.1)	0.036	0.037
B3galt3 (b3GT3)	**3:** 37[e]	D3Mit282 (30.6) D3Mit348 (42.6)	0.023	0.033
B3galt4 (b3GT4)	**17:** 18.4	D17Mit104 (10.9) D17Mit216 (25.1)	0.192	0.089
Camp (Cramp)	**9:** 61.0	D9Mit115 (54.6) D9Mit82 (67.8)	0.096	0.098
Cd14	**18:** 31.0	D18Mit206 (25.1) D18Mit143 (36.1)	0.074	0.081
Ctgf (fisp-12)	**10:** 17.0	D10Mit106 (12.0) D10Mit196 (23.0)	0.026	0.030
Dfy	**1:** 94.0	D1Mit370 (86.3) D1Mit166 (99.5)	0.158	0.097
Fau	**19:** 3.0	D19Mit29 (1.1) D19Mit16 (13.1)	0.078	0.083
Fut1	**7:** 23.2	D7Mit80 (15.3) D7Mit260 (28.4)	0.051	0.048
Fut2	**7:** 23.2	D7Mit80 (15.3) D7Mit260 (28.4)	0.051	0.048
Fut4	**9:** 3.0	D9Mit43 (2.2) D9Mit205 (13.1)	0.043	0.039
Hoxa2 (Hox-1.11)	**6:** 26.29	D6Mit186 (20.8) D6Mit177 (31.7)	0.048	0.048
Nppb (BNP)	**4:** 76.5	D4Mit49 (71.0) D4Mit256 (82.0)	0.131	0.130
Psmb10 (MECL1)	**8:** 51.0	D8Mit182 (44.8) D8Mit314 (56.8)	0.093	0.044
Sec1-pending (sec1)	**7:** 23.2	D7Mit80 (15.3) D7Mit26 (28.4)	0.051	0.054
Sox15	**11:** 39.0	D11Mit276 (33.9) D11Mit356 (48.1)	0.050	0.038
Tnf	**17:** 19.06	D17Mit104 (10.9) D17Mit216 (25.1)	0.192	0.086
Wnt1	**15:** 56.8	D15Mit73 (50.3) D15Mit160 (62.3)	0.120	0.072

[a] Genetic map position from Mouse Genome Resources of the National Center for Biotechnology Information (USA; NCBI) unless indicated.
[b] Markers used to estimate recombination rate. Data from Van Etten et al. (1999).
[c] Recombination rate estimated using data from Van Etten et al. (1999).
[d] Recombination rate from Nachman and Churchill (1996), converted approximately to an equivalent scale of cM/cR in Van Etten et al. (1999).
[e] Genetic map position estimated through the use of the Celera Discovery System and Celera Genomics associated databases.

of past hybridization between *M. m. musculus* and *M. m. castaneus* (Yonekawa et al. 1988). Nevertheless, a subdivided population model with a low migration rate probably fits the data best, and thus provides a good opportunity to study the effects of population subdivision.

The estimated local recombination rate (cM/cR) of each locus is shown in table 2. There is another independent estimate of rates of recombination by Nachman and Churchill (1996) calculated from the density of markers on the genetic map. They are converted approximately to an equivalent scale of cM/cR (1 cR = 100 kb; Van Etten et al. 1999), and are also listed in table 2. These two estimates are highly correlated ($r = 0.72$, $P < 0.001$, Spearman's $P < 0.001$), but because our estimate in cM/cR uses more recent information on the mouse genome, we decided to use it for the following analyses.

The number of silent sites used for the analyses, nucleotide diversities, G_{ST}, and divergence of each locus are listed in table 3. The nucleotide diversity of the pooled sample (π total) of each gene is plotted against the recombination rate of its region in fig. 1*A*. There was no correlation detected between these two variables (fig. 1*A*; $r = 0.06$, $P = 0.83$; Spearman's $P = 0.47$). A possible reason for the lack of correlation is that the regional variation in recombination rate for mouse seems to be much lower than that for *Drosophila* or for human (data from Nachman and Churchill 1996; Payseur and Nachman 2000). Alternatively, the population structure of mice could have prevented advantageous alleles from spreading throughout the range of all subdivided populations, assuming genetic hitchhiking as the primary cause of the correlation. In this study, we focused on investigating the latter possibility.

Table 3
Nucleotide Diversity of the 19 Loci Analyzed in This Study

Symbol	Length (bp)	Number of Silent Sites				Within Sub-population[b]	d[c]	G_{ST}[d]	Divergence[e]
		Synonymous	Intron (bp)	π Total (bp)	π Total[a]				
B3galt1	917	208	0	208	0.0180	0.0072	0.0198	0.60	0.0000
B3galt2	1228	282	0	282	0.0039	0.0009	0.0044	0.77	0.0142
B3galt3	996	228	0	228	0.0124	0.0055	0.0135	0.56	0.0044
B3galt4	1112	292	0	292	0.0070	0.0077	0.0068	−0.11	0.0171
Camp	987	81	672	753	0.0022	0.0010	0.0024	0.55	0.0173
Cd14	1254	254	0	254	0.0089	0.0059	0.0094	0.33	0.0158
Ctgf	1156	82	371	453	0.0038	0.0000	0.0044	1.00	0.0110
Dfy	1509	252	462	714	0.0146	0.0081	0.0156	0.45	0.0056
Fau	1241	102	826	928	0.0067	0.0059	0.0068	0.11	0.0075
Fut1	1134	277	0	277	0.0101	0.0081	0.0104	0.19	0.0036
Fut2	963	234	0	234	0.0021	0.0021	0.0021	0.00	0.0336
Fut4	1170	309	0	309	0.0047	0.0000	0.0058	1.00	0.0097
Hoxa2	907	280	0	280	0.0000	0.0000	0.0000	NA	0.0000
Nppb	1112	87	672	759	0.0094	0.0079	0.0096	0.16	0.0105
Psmb10	652	174	0	174	0.0028	0.0024	0.0029	0.15	0.0039
Sec1-pending	1107	39	478	517	0.0162	0.0063	0.0179	0.61	0.0036
Sox15	1340	292	553	845	0.0024	0.0006	0.0027	0.75	0.0024
Tnf	1201	63	926	989	0.0045	0.0051	0.0044	−0.12	0.0091
Wnt1	1044	86	714	800	0.0061	0.0022	0.0061	0.64	0.0075

[a] Average number of pairwise nucleotide differences per site calculated from all 28 (21 for *Fut4*, see text) combinations of strains.
[b] Average number of pairwise nucleotide differences per site between the sequences of the four (three for *Fut4*, see text) pairs of strains from the same subpopulations.
[c] Average number of pairwise nucleotide differences per site between the sequences of the 24 (18 for *Fut4*, see text) combinations of strains from different subpopulations.
[d] Nei's (1973) estimation of F_{ST} (G_{ST}).
[e] Divergence between *M. musculus* and *M. spicilegus*.

We first calculated π within subpopulations and d, and plotted them against the recombination rate (fig. 1*B* and 1*C*, respectively). A positive correlation was detected between recombination rate and π within subpopulations (fig. 1*B*; $r = 0.46$, $P = 0.045$; Spearman's $P = 0.019$), but not between recombination rate and d (fig. 1*C*; $r = 0.01$, $P = 0.97$; Spearman's $P = 0.54$). We then examined the correlation between the recombination rate and the level of nucleotide differentiation among subpopulations (G_{ST}). There was a signification negative correlation, as shown in figure 1*D* ($r = -0.64$, $P = 0.0034$; Spearman's $P = 0.0061$). This was the clearest pattern in terms of the significance level in our analyses. The hitchhiking or background selection in a subdivided population is expected to increase the genetic differentiation between subpopulations in regions of low recombination (Charlesworth, Nordborg, and Charlesworth 1997; Slatkin and Wiehe 1998). Hence, our analyses suggest that these forces are acting in this structured population.

Recently, it has been suggested that an additional factor unrelated to natural selection contributes to the correlation between recombination rate and nucleotide variation. Lercher and Hurst (2002) claimed that the correlation observed in the human genome was due, at least in part, to a higher mutation rate in regions of high recombination because it holds for single-nucleotide polymorphisms (SNPs) across the entire human genome, the great majority of which are not near exons or control elements. If this increased mutation rate is a major factor, a positive correlation is expected between recombination rate and divergence among closely related species. Hellman et al. (2003) showed a positive correlation between recombination rate and human-chimp as well as human-baboon divergence. Their findings support the neutral explanation for the phenomenon in humans. In contrast, our data showed no correlation between recombination rate and divergence between *M. musculus* and *M. spicilegus* (fig. 1*E*; $r = 0.11$, $P = 0.65$; Spearman's $P = 0.38$), which diverged within several million years (She et al. 1990; Moriwaki, Shiroishi, and Yonekawa 1994). The exclusion of the outlier (*Fut2*; 11) in figure 1*B*, which has extremely high levels of divergence, would not reveal any significant pattern ($r = 0.32$, $P = 0.20$; Spearman's $P = 0.28$). Genetic variation between subpopulations (d), which must have diverged much later after the *M. musculus* and *M. spicilegus* divergence, also had no correlation with the recombination rate (fig. 1*C*). Thus, our data indicate that any determinants of mutation and/or substitution rates in mice do not have a comparable effect on diversity and divergence.

However, we should be cautious about interpreting our results. First of all, the recombination rate estimates used in our analyses are only from *M. m. domesticus*. There is not yet sufficient information on the map distances of other subspecies or closely related species to know whether they are consistent. Second, the sequence data we used are located in close proximity to functional genes, and the whole non-functional region of the genome has not been analyzed. Finally, the sample size in terms of base pairs and number of individuals is not comparable in scale to the study of Hellman et al. (2003), which found a weak correlation between divergence and recombination that can account for the relationship between nucleotide diversity and recombination in human. In contrast, even

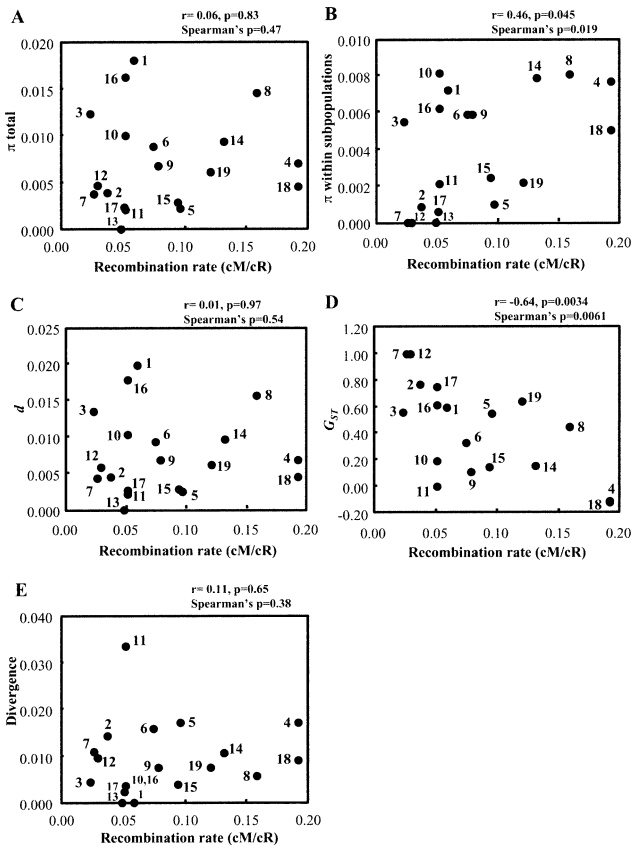

FIG. 1.—Scatterplots of recombination rate versus nucleotide variation calculated from the sequences of eight inbred strains of *Mus musculus* (see table 1) and one *M. spicilegus* strain for each of the 19 autosomal loci (see table 2). The sequence data of the *Fut4* locus suggested an introgression from other distant taxa in BLG2 strain (Liu, Takahashi, Kitano, Koide, Shiroishi, Moriwaki, and Saitou, unpublished data); thus this strain was excluded from the analyses of this locus. *A*. Recombination rate versus π total, which is the average number of pairwise nucleotide differences per site among all the 28 (21 for *Fut4*) combinations of strains. *B*. Recombination rate versus π within subpopulations, which is the average number of pairwise nucleotide differences per site between the sequences of the four (three for *Fut4*) pairs of strains within the same subpopulation. *C*. Recombination rate versus *d*, which is the average number of pairwise nucleotide differences per site between the sequences from the 24 (18 for *Fut4*) combinations of strains from different subpopulations. *D*. Recombination rate versus level of nucleotide differentiation among subpopulations (G_{ST}; Nei 1973). Because π total of *Hoxa2* was 0, this locus was excluded from the calculation of G_{ST}. *E*. Recombination rate versus nucleotide divergence between *M. musculus* and *M. spicilegus*. The numbers beside the plots indicate gene symbols as follows; 1: *B3galt1*, 2: *B3galt2*, 3: *B3galt3*, 4: *B3galt4*, 5: *Camp*, 6: *Cd14*, 7: *Ctgf*, 8: *Dfy*, 9: *Fau*, 10: *Fut1*, 11: *Fut2*, 12: *Fut4*, 13: *Hoxa2*, 14: *Nppb*, 15: *Psmb10*, 16: *Sec1-pending*, 17: *Sox15*, 18: *Tnf*, 19: *Wnt1*.

a large data set of 255 *Drosophila melanogaster* and *D. simulans* loci revealed no detectable relationship between divergence and recombination rate (Betancourt and Presgraves 2002). A larger-scale analysis is awaited to know which of these cases applies for the mouse data. However, all the above concerns would not weaken the evidence of the correlations actually detected in this study, if at most they might veil a weak existing relationship. In conclusion, our analyses of a structured population of mice showed that the effect of genetic hitchhiking or background selection may still play a dominant role in shaping the positive correlation between recombination rate and genetic variation in many genomic regions of this species.

Acknowledgments

We thank Michael Nachman for providing us with the exact numerals of recombination rates for all the gene regions. We also thank Toshiyuki Takano-Shimizu, Jeff Wall, and Hiroshi Akashi for valuable discussions. We are grateful to Justin Fay for his suggestions to improve the manuscript. This study was supported by grants-in-aid for scientific studies from the Ministry of Education, Science, Sports, and Culture, Japan, to N.S., and a Japan Society for the Promotion of Science Research Fellowship for Young Scientists to A.T.

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Accepted September 29, 2003