


RENEWAL PROPOSAL

MUTATION RATES AND MUTATIONAL LOADS IN MAN

L. L. Cavalli-Sforza  
Department of Genetics  
Stanford University Medical School  
Stanford, California 94305

Application Date: June 18, 1974

Prepared for the U.S. Atomic Energy Commission, Division of  
Biology and Medicine, under Contract Number AT(04-3)-326,  
Project Agreement Number 34.



---

L. L. Cavalli-Sforza  
Professor of Genetics

## AEC GRANT RENEWAL

### I. Sex Ratio Data

We have received from the Italian Statistical Institute tapes of the 1962 census for the provinces of Siena (central Italy) and Catanzaro (southern Italy). The study, started in the province of Verona (northern Italy), will be continued with this new data.

### II. Analysis of Parish Book Data

The preliminary analysis of inheritance of longevity should be continued. Further, now that a partially linked file is available data on fertility and twinning are obtainable and analysis may be started on these data.

### III. Consanguinity

It is hoped that a monograph on Italian consanguineous marriages will be written by the principal investigator with A. Moroni and others. Statistical tables for this book are now fully ready.

### IV. Human Evolution

a) Ethnic variation. We would like to extend with D. Wagener the analysis of ethnic variation in genetic disease to dominant diseases. It is not clear if the numerical data will be found, but a literature search will be started with this aim in mind.

b) Pygmy demography and effects of acculturation on birth rates.

A new expedition to the Central African Republic is planned with a purpose to continue studies on the Pygmies. A further reason for this trip will be to help a group of psychologists headed by Dr. H. Witkin

(Educational Testing Service, Princeton, N.J.). Work on demography will be continued. Included in this study will be death and birth rates as well as the change in birth rates which is expected to occur with the transition to agriculture. As several groups, previously identified, have effected this transition to agriculture, it is of interest to test if the expected changes do occur. The budgeted expenses are estimated for travel between San Francisco and Bangui (capital of the Central African Republic) and living expenses for one month for one person.

PROPOSED BUDGET

October 1, 1974 to September 30, 1975

Mutation Rates and Mutational Loads in Man

L. L. Cavalli-Sforza  
Principal Investigator

PERSONNEL:

L. L. Cavalli-Sforza Principal Investigator	10%	\$ 3,800	
Albert Ammerman (Anthropologist)	25%	2,500	
Carlo Matessi (Geneticist)	50%	6,000	
4 Graduate Students (\$500 each)	100%	<u>2,000</u>	
TOTAL SALARIES		14,300	
Staff Benefits (18%)		<u>2,574</u>	
TOTAL PERSONNEL			\$16,874
Computer Time: Stanford University			4,000
Travel: (Foreign) for 1 person (see IV b)			1,500
Publication expenses			<u>500</u>
TOTAL DIRECT COSTS			\$22,874
Indirect Costs @47% NTCB			<u>10,751</u>
TOTAL AMOUNT REQUESTED			\$33,625


ANNUAL PROGRESS REPORT OF SCIENTIFIC ACTIVITY  
FOR PERIOD OCTOBER 1, 1973 through SEPTEMBER 30, 1974

Report Date: June 18, 1974

Mutation Rates and Mutational Loads in Man

L. L. Cavalli-Sforza  
Department of Genetics  
Stanford University Medical School  
Stanford, California 94305

Prepared for the U. S. Atomic Energy Commission, Division of Biology  
and Medicine, under Contract Number AT(04-3)-326, Project Agreement  
Number 34.

  
\_\_\_\_\_  
L. L. Cavalli-Sforza

## AEC PROGRESS REPORT

### I. Sex Ratio Data

Data of the 1962 Italian census were analyzed for the correlation between the sex ratio of a woman's progeny and the age of the maternal (and paternal) grandfather at the time of the birth of the woman (G. Zei and L. Cavalli-Sforza). This correlation was earlier given as a method of estimating sex linked recessive lethals. Earlier results were contradictory. The new data from the census of the province of Verona (about one million people) gave negative results (no correlation). More data will be forthcoming.

### II. Analysis of Parish Book Data

A correlation table for the age at death of parents and children of the Parma Valley project have now become available. These data include records for three centuries. This is a first major result of the record linkage project (presently being carried out by M. Skolnick, now of Utah State University, in collaboration with us and, at Parma, E. Siri and A. Moroni). There are some fairly weak correlations, weaker than would have been anticipated from the literature, which is, however, mostly extremely old. The analysis will require special techniques because of the complicated distributions of the age at death and their change through time.

### III. Consanguinity

A paper has now been written by Prof. Crumpacker of the University of Colorado on the subject of the use of road and air distances for the study of isolation by distance. Consanguineous marriages were also studied as a function of distance.

#### IV. Human Evolution

##### a) Ethnic Variation for Recessive Disease

An analysis of gene frequency data for some recessive diseases was carried out with D. Wagener to estimate the possible roles of drift, linkage, mutation and selection in establishing ethnic variation of these diseases. Three diseases were used for this study, phenylketonuria (PKU), cystic fibrosis and Tay-Sachs, for which there is a fair amount of reliable data encompassing several ethnic groups and which all show considerable ethnic variation.

To determine the possible role of drift in determining variation, a solution was obtained for the moments of Wright's distributions of gene frequencies in populations of size  $N$  and mutation rates  $\mu$  (1). From these moments the mean gene frequency and Wahlund's variance (a measure of inbreeding) were determined and compared to the same statistics generated from observed data. The variation observed for PKU between racial groups fell within the variation calculated for large populations due to drift. However, the variation for cystic fibrosis appeared to be relatively higher than expected. Tay-Sachs, displaying a markedly high variation, was not entirely explained by this method, but probability of deviations from the expectations are being calculated to see if this variation is nevertheless within reason with respect to a drift explanation. We are not certain that the approximate solution recently offered by Rao and Morton (2) is satisfactory for a recessive lethal.

Cystic fibrosis, as mentioned above, showed a relatively high racial variation. This observation coupled with recent reports of an association of a particular Caucasian Gm haplotype with cystic fibrosis patients

prompted the analysis of non-equilibrium linkage and epistatic models to generate high variation in gene frequencies. A "hitchhiking model" was studied in which a deleterious recessive is linked to a locus with an advantageous allele (e.g. a Gm haplotype). The magnitude and duration of the increase in the recessive deleterious allele were studied. Similar increases, resulting in permanent changes in gene frequencies, may be generated by unlinked epistatic interactions which were also studied. This may turn out to be the case for cystic fibrosis and Gm.

While this analysis does not rule out possibilities of differences in mutation or selection rates, it does describe the magnitude of effects from drift, linkage or epistasis.

b) Analysis of Trees.

Tree analysis of 35 human populations for 58 alleles (including data from the HL-A Workshop) was carried out by L. Cavalli-Sforza and A. Piazza. This study provided an occasion for radical revision of the theory and methodology. A method borrowed from multivariate analysis can test "treeness", that is, the existence of a pattern in the matrix of variances and covariances of populations corresponding to the expected if drift (random or selection) is important. Constant selection (equal for all populations) does not affect treeness. However, convergent and divergent selection will reduce treeness. Hybridization effects can also be clearly demonstrated by the appropriate analysis. Presently available methods have been shown to depend on the hypothesis of constant evolutionary rates, which is frequently wrong; but the methods now developed are free from such bias. The theoretical and numerical work in this problem has been



time consuming, but the results have been rewarding in our judgment and two manuscripts, one on the theory and the other on the actual data analysis, are now almost finished.

c) In a paper presented by Ammerman, et al. to a symposium on Human Biogeography at the Smithsonian, the work on growth and migration models of Neolithic populations was summarized. Interpretations of growth and migration as local events and possible techniques for the reconstruction of these parameters in specific cases were also discussed.

Research papers resulting from this project:

Cavalli-Sforza, L. L. 1973. Origin and Differentiation of Human Races (Huxley Memorial Lecture). Proc. Royal Anthropological Inst. of Great Britain and Ireland, pp. 15-25.

Cavalli-Sforza, L. L. 1974. The Role of Plasticity in Biological and Cultural Evolution. New York Acad. of Sci. 231:43-59.

Kidd, K.K. and Cavalli-Sforza, L.L. 1974. The Role of Genetic Drift in The Differentiation of Icelandic and Norwegian Cattle. Evolution (In press).

Sgaramella-Zonta, L. and Cavalli-Sforza, L.L. 1973. A method of the detection of a demic cline. Proceedings, Workshop on Population Structure, Hawaii University Press, pp. 128-135.

Yasuda, N., Cavalli-Sforza, L.L., Skolnick, M. and Moroni, A. 1974. The evolution of surnames. An analysis of their distribution and extinction. Theoretical Population Biology 5:123-142.

Cavalli-Sforza, L. L. and Piazza, A. 1974. Analysis of Human Evolution. I. Evolutionary Rates, Independence and Treeness. Am. J. Hum. Genet. (submitted for publication).

Piazza, A., Sgaramella-Zonta, L., Gluckman, P., Cavalli-Sforza, L. 1974. Analysis of Human Evolution. II. Phylogenetic analysis of a sample of 35 human populations tested for HLA and other markers. Am. J. Hum. Genet. (in preparation).

Cavalli-Sforza, L. L. 1974. Human Population Genetics. Scientific American (in press).

Ammerman, A., Cavalli-Sforza, L. and Wagener, D. 1974. Towards the Estimation of Population Growth in Old World Prehistory. Proc. Soc. for American Archaeology, Smithsonian Inst., May, 1974.

FISCAL DATA FOR CURRENT BUDGET PERIOD

October 1, 1973 to September 30, 1974

BUDGET CATEGORIES	AWARDED	ACTUAL EXPEND. 05/31/74	ESTIMATED EXPEND. REMAINDER BUDG. PER.	TOTAL	BALANCE
Salaries/St. Benef.	\$17,201	\$3,413	\$10,779	\$14,192	\$3,009
Computer Time	4,083	\$6,936		6,936	-2,853
Others	500	656		656	- 156
	<u>\$21,784</u>	<u>\$11,005</u>	<u>\$10,779</u>	<u>\$21,784</u>	<u>0</u>
Indirect Costs	\$10,238	5,282	4,956	\$10,238	0
	<u>\$32,022</u>	<u>\$16,287</u>	<u>\$15,735</u>	<u>\$32,022</u>	