A family affair

Consanguinity, Inbreeding and Genetic Drift in Italy

by Luigi Luca Cavalli-Sforza,
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More is known about natural populations of humans than of any other species. There are records, usually publicly available, about the geographic distribution of populations, their demography and patterns of migration and mating, and often about how these vary with time. These are the factors that affect the population distribution of genetic variability, generally subsumed under the definition of population structure.

When the distribution of genetic variation can be explained by the population structure, it can be assumed that natural selection has not played a role in determining the distribution, at least within the limits of detectability. This effect should be the same for all 'neutral' genetic variation, so when variation is significantly heterogeneous, as pointed out nearly 40 years ago by Luca Cavalli-Sforza, this is evidence for the existence of natural selection. The determination of population structure is therefore an important goal for human population genetics. This has been emphasized recently by the need for carefully chosen control populations for disease association studies involving large numbers of DNA polymorphic markers. Small relative risks may easily be masked, or apparently created, by hidden population structure, leading to numerous false positive or negative associations.

Cavalli-Sforza and his colleagues in Italy have spent more than 50 years studying human population structure and its consequences. This extraordinary book, packed with detailed information, is their account of this work.

The initial stimulus was the opportunity to access the extensive records of the Catholic church on dispensation for marriages between close relatives (consanguineous marriages). These data allowed estimates of the frequency of marriages between cousins, for example, or between an uncle and his niece, and through that the extent of population inbreeding and its effects. The first studies made use of parish records in the Parma valley, but later ones used the Vatican's archives covering the whole of Italy.

The world-wide variation in consanguineous marriages is surprising: there is a high frequency in many Arab Muslim populations, even though the Koran condemns marriages between close relatives, as does the Judæo-Christian tradition. The dispensation data do not always record marriages

Kissing cousins? Italian marriage registers have revealed the frequency of human inbreeding.

between more distant relatives, so they may underestimate the level of inbreeding by as much as a factor of five.

However, a great deal of information can be obtained from the relative frequencies of the different types of matings, and the way they change over time. These frequencies are affected by the difference in age between husband and wife, by the tendency in a more or less stable population for a woman to move to her husband's locality, and by whether women rather than men try and arrange marriages. Marriages between an aunt and her nephew are much less common than those between an uncle and his niece.

For marriages of equal lineage, for example between first or second cousins, it is the number of males and females in the lineage that affects their relative frequency: the more males there are, the less the effect of migration and the commoner the type of marriage. Perhaps counterintuitively, increasing the population size may raise the proportion of consanguineous marriages, as long as migration does not increase. In the first quarter of the twentieth century there was a slow increase in the rate of consanguineous marriages, but this decreased as industrialization and improved transport and communication increased the rate of migration.

Detailed theoretical modelling, especially computer simulation, shows that the frequencies of the different types of mating between relatives are essentially as would be expected if they occurred by chance. Inbreeding does not seem to be specifically avoided, as is often presumed, because of its negatively perceived effects in uncovering deleterious recessives. However, marriages between brother and sister are prohibited in most cultures, and there is a similar avoidance of matings between members of the same kibbutz in Israel.

Surnames behave as surrogate genetic markers on the Y (male-determining) chromosome. Cavalli-Sforza and colleagues use extensive data from telephone directories to obtain a distribution of surnames throughout Italy. They use this to estimate the key parameters of population structure and show that these, on the whole, match those obtained using genetic markers. These and other studies suggest that most of the common blood-group-determined polymorphisms can be explained by genetic drift in the absence of natural selection, at least in the populations studied. The authors conclude that, even with the extensive DNA data now available, there is no conclusive evidence that natural selection affects common polymorphisms.

This is surely not the case. The variation observed in the HLA alleles, for example, is so unevenly distributed along the gene, matching regions of functional significance and mostly due to non-synonymous substitutions, that this alone, following Cavalli-Sforza's own suggestions, must be due to selection. The fact that most polymorphisms detected by random screening of DNA sequences of genes are synonymous, or occur in introns, points in the same direction.

A careful reading of this remarkable book will yield much more information. More diagrams and histograms would have helped readers to digest the mass of data, and better copy-editing would also have been useful.

In commenting on the value of parish registers in England for a more satisfactory study of surnames, the authors say: "Here is a task for an ambitious and dedicated organiser." It is hard to imagine that anyone could be more dedicated than Cavalli-Sforza, Moroni and Zei.

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