International Journal of Human Sciences
ISSN:1303-5134

Volume: 9 Issue: 2 Year: 2012

# Demogenetic study – A holistic approach for studying population structure

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**Abstract**
Demography and population genetics, though they have emerged as separate disciplines, tried to explain the population structure in each own way. Here in this article, the interrelationship between these disciplines are reviewed with reference to the population structure. The correlation and interdisciplinary between these two disciplines in explaining the population can be discussed under three different approaches i.e. demography, evolutionary and epidemiology. Both the demographic and evolutionary parameters are interrelated. The demographic parameters are influenced by genetic factors and in return the evolutionary fate of a population is explained through demographic parameters – fertility and mortality. This correlation is more evident in epidemiological approach. Nowadays with the rise of complex disorders among the interbred populations, the complete understanding of the population structure is much needed.

**Keywords**: Population structure; Eugenics; Coalescent; Demogenes; Stratification.

## Introduction

Anthropological insight has been increasingly applied in the present modern researches, as different disciplines have shifted the research areas into the human related topics like public health, human evolutionary biology, human genetics, etc. Even non-anthropological scholars have also started studying the human population groups, and therefore it can be assumed that that anthropological research holds an important place in the modern era. Such anthropological study of a particular

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community or population group – mainly the primitive ones – has been an important area of interest since long time. Different anthropologists have tried to understand a particular community i.e. human population structure through different approaches- genetic, demographic, socio-cultural, etc. In fact, a population size/structure is determined by both genetic and demographic parameters including socio-cultural patterns. Genetic structure of a population is the way genes are organized into genotypes in the populations and the extent to which individuals share a common gene pool which shows the degree of biological relatedness among the members. While, demographic structure of a population is the distribution of fertility and mortality, emigration and immigration patterns, and the effects of these parameters on the age and sex composition of the population (Harrison and Boyce, 1972). Thereby, genetic variables such as mutation, selection, gene flow, genetic drift, etc. in a population over time may change the genetic constituents of the population. And at the same time, demographic variables like fertility, mortality, morbidity and socio cultural factors like marriage and migration are also responsible for the structural change of the population and dissimilarities that exist between different population groups. In this way, these two disciplines – demography and genetics – have tried to explain the human population dynamics separately, in each own ways.

However, historically, the study of human population growth and distribution has had very close ties with the theory of human evolution (Lewontin, 1965). Darwin's theory of natural selection was also inspired by the Malthusian theory of exponential population growth (Cavalli-Sforza, 2007). Both these disciplines – demography and genetics - share inter disciplinary approach in methodological framework too. Sutter (1958) outlined the importance of the demographic frame of reference for genetic studies. Geneticists required a diverse range of data on race, age, sex, marital status, nativity, socio-economic status, intelligence, diseases and migration. The demographers in return could provide these data through census statistics, hospital data and surveys of consanguineous marriages and assortative matings. The difference between these two disciplines lies in the fact that while demography, according to Malthusian theory, 'naturally' focuses to the problem of large-scale population growth and its relation with socio-economic variables, geneticists, following the steps of Darwin, are more concerned about the genetic variations among the population groups (Adams, 1990). In demography, the study of a community's population structure in terms of age and sex distribution centers around the female population only as the female procreates the future generation but the interaction between the two sexes – male and female – is more important in Mendelian population genetics. Despite their shared history, commonness and differences, both geneticists and demographers move on different directions as separate disciplines and there is a lack of interaction between these two disciplines (McNicoll, 1992).

From 1920 onwards, the emphasis has been given to bring about the works of both genetics and demography together through population studies, especially under the umbrella of 'eugenics', for facilitating the social and biological approaches to understand human problems. It was Frederick Osborn (1889-1981), a demographer and eugenist who took the main responsibility for the same. His efforts succeeded in materializing the concept of 'genetic demography' under the American Eugenic Society (AES) in 1960s, where leaders from both disciplines decided to carry out various research programs on the concept. Ramsden (2008) defined the new concept 'genetic demography' as the study of evolutionary causes and consequences of breeding structures and process of mate selection in human population. According to Osborn and Bajema (1972), two major developments are essential in bringing up the interdisciplinary research between genetics and demography. First, it is to make demographers appreciate the genetic consequences of population dynamics. Demographers are needed to focus upon the selection of traits and characters that are biologically significant: the study of fertility differentials within the social classes, rather than between the social classes. Second, it is to make geneticists aware of the genetic significance and eugenic potential of socially determined fertility dynamics.

In this review, an attempt has been made to understand the correlation between these two disciplines – genetics and demography – and their inter relationship, a holistic view, in understanding to explain the human population dynamics. It is likely, that a combined approach of these two disciplines would be able to suggest a more precise and meaningful perception of a population group, though both the disciplines try to explain the human population dynamics in each own. These inter relationships can be discussed in terms of demographic, evolutionary and epidemiological approaches.

**Approach for understanding human population structure**

**Demographic approach**

Demography is the study of the changes in population size and composition through socio-cultural variables like births, deaths, marriages, migration, etc. in a community over a period of time. It defines the makeup of a particular human population through socio-cultural aspects affecting the population structure. In addition, it has very close ties with anthropology where it can be defined as a part of anthropology which also deals with the statistics of births, deaths and diseases, etc. Both the subjects are concerned with the study of human mating patterns, mutation and gene flow (Raj, 2006).

Fertility is one of the important socio-demographic parameters which measure the rate of population growth. Fertility is a fitness component that emerges inherently from the interaction of a mating pair of individuals (Templeton, 2006). By fertility inheritance, we mean that a positive

correlation is observed between the numbers of effective children of an individual and the number of effective children of his/her parents, the effective children being the children that reproduce in their own population. It involves genetic variance - differences in the genetic makeup of individuals affecting their fertility (Rodgers, 2001). Fertility differentials are also genetically influenced. The important common measures of genetic influence on fertility are the heritability co-efficient ($h^2$) and the genetic co-efficient of variation (CVa). $h^2$ measures the percentage of overall variance (often referred to as phenotypic variance) in some physical traits or behavioral characteristics that are related to genetic processes, while CVa is (mean standardized) direct measure of the genetic variance of the traits being measured. About half of the total genetic variance in fertility can be explained by genetic variance in waiting time to pregnancy (Rodgers et al, 2003).

MacMurray et al (2003) proposed the most likely genetic outcome of rapid fertility decline in the populations – i) alleles that have been maintained in populations by so-called fertility compensation for variability in specific disease risk will increase in frequency when the mortality risk of the respective disease sinks. ii) genetic polymorphisms having relevance to sexual behavior and childbearing motivation will experience a vastly changing selection pressure. As for example, they found that the carriers of DRD2 *TaqI* A1 negative allele in both heterozygote and homozygote conditions among the Mayan Indian population had their first child later in life. Gloria-Bottini et al (2003) have also found an association of decreased fertility with G6PD deficiency among the Sardinian population. Women carrying the gene for G6PD deficiency, i.e., in heterozygotic carriers, have decreased fertility.

Mortality is another important demographic factor which affects and influences both fertility and birth rate which in turn make an alarm on the selection intensity. Selection intensity is defined as the difference between the mean selection criterion of those individuals selected to be parents and the average selection criterion of all potential parents, expressed in standard deviation units. Mortality is also an indicator of the health status of a population. When mortality rate in any population is high, it affects not only the population structure by numbers; it also alters the genetic composition of the population. Fitness, which is a demographic property, is a function of the fecundity and mortality variables of the individuals in the population. The intensity of natural selection which is analytically described by the sensitivity of Darwinian fitness, changes due to the age-specific fecundity and mortality variables (Demetrius et al, 2007). High prevalence of morbidity in any particular community, due to certain complex disorders or recessive genetic disorders also affects the demographic dynamics of a population group, by enhancing the mortality rate. Further, it also has effect on the genetic composition of the population. Spread of epidemic in such population further facilitates in the selection of traits that have higher survivality.

Socio-economic changes may substantially and often deleteriously affect population structure. Irregular changes in the sizes of the human population groups may alter their genetic structure irrespective of their adaptability to dramatic changes in the environment including the social environment (Lavryashina and Ulyanova, 2005). Mating within the sub-population alters the distribution of genes upon which selection acts, thereby further modifying the genetic structure of the population (Osborn, 1956). Through a combination of the two processes of assortative mating and differential fertility, the frequency as well as the distribution pattern of the genes will be altered.

**Evolutionary approach**

A population group is never static; it constantly changes through certain natural forces. The evolutionary aspect of a population could be explained through population genetics, which holds an important central place in evolutionary biology. Population genetics is a field of biology that studies the genetic composition of biological populations and the changes in genetic composition that result from the operation of various factors, including natural selection. Hardy-Weinberg theorem which is considered as the founding principle of population genetics, was re-explained in World Population Conference (1953), as assortative mating, as social and psychological factors affecting variations in fertility, as variations in age of marriage and other factors for which the demographic parameters should be able to explain (Osborn, 1953).

The important evolutionary forces that explain the future course of any population group – natural selection, genetic drift, migration and mutation – can be explained through the demographic concept. Natural selection is a matter of differences among inherited types in probability of survival to reproduction age, and fertility (Cavalli-Sforza, 2007). Natural selection is based on differential DNA replication in the context of the environment in which individuals live, mate and reproduce. Fitness or Darwinian Fitness (according to Fisher, 1930) is the genotypic value of the individual fitnesses of a group sharing a common genotype (Templeton, 2006). This Darwinian fitness describes the capacity of a variant or mutant type to invade and become established in a resident population.

Unevenness of genetic contributions to the next generation induced by natural selection will alter the gene pool of the next generation (population). Natural selection, thereby, tends to alter the gene pool of a population group rather than an individual's in a manner that increases the average reproductive fitness of the population further leading to the microevolutionary processes. And it is measured by the fertility and mortality rates of different genotypes. According to Fisher (1930), the rate of increase of fitness of any organism at any time is equal to its genetic variation in fitness at that time. Thus, differences in fertility and mortality levels in various groups in a population are of great significance in understanding the structure of a population.

Genetic drift is also one of the evolutionary forces that can alter the genetic makeup of a population groups through time. It is a matter of the number of randomly reproducing individuals in a small population group and of variation in the number of children (Cavalli-Sforza, 2007). The impact of drift is more pronounced in small population where fixation or loss of genes takes place as the population sizes fluctuate from a very few to subsequent population growth over two or more generations. Hence, the differential fertility in such populations is effective for the evolution of the group. Migration is another demographic quantity which promotes the chances of gene flow among different population groups. Migration can be of two types – individual migration and group migration (Cavalli-Sforza, 1973). Individual migration generally takes place through social norms like marriages between the groups and is usually limited to short ranges. It typically decreases the variation among populations generated by drift, or by natural selection in different environments. Group migration leads to colonization of new areas, which may have opposite effects, being likely to generate new drift through what is called "founder effect". Founding a new group generates further opportunities for drift because of the usually small numbers of individuals in generations following that of the founders. It may also give rise to new patterns of genetic variation because of natural selection in the new environments experienced by the migrants (Cavalli-Sforza, 2007).

Mutation is the fourth evolutionary factor that can also be described in demographic terms; although, it is the one for which it is most difficult to get good estimates because it occurs rarely (Cavalli-Sforza, 2007). It is the source of all the evolutionary novelties which lead to the variation among individuals and population groups. These variations with the influence of other evolutionary factors, give way to inter or intra population divergences which would further facilitate the evolution of the group. These four evolutionary factors interact with each other in different ways. Natural selection is responsible for the fixation of the variation induced by mutation in response to the environment. Selection of the heterozygotes increases the stability of the variation. Drift wipes out the variation and differentiate the population from one another to other; while individual migration mostly tend to redistribute the existing variation within or among the Mendelian population groups.

The human migration and its demographic expansion throughout the globe can also be explained through analysis of genetic variation among different groups which is more clearly defined in the genomic era. Haplotypes reconstruction at different sites comprising an entire gene or a DNA region of interest, have been applied for constructing trees for phylogeographic analyses. Haplotype is a multisite haploid genotype at two or more polymorphic sites on the same chromosomal region (Templeton, 2005). An increase in the rate of decay of linkage disequilibrium outside of Africa

results to deviation of haplotype frequencies from being in equal proportions due to recombination (Kruglyak, 1999); and it has been cited as evidence for a replacement model of modern human evolution (Tishkoff et al, 1996). Further, the evolution of haplotype systems is bound to have been shaped by interaction of population history, mutation, recombination, all with a significant chance component (Calafell et al, 2001).Their relative distributions among different populations hint at the migratory route of the population of interest, more accurately than that of the single individual allele distribution through the extent of genetic diversity and similarity among these populations.

The human genetic diversity patterns among different world population groups provides a glimpse of population's history as each major demographic event leaves an imprint on a population's collective genomic diversity (Jorde, 2003). A reduction in population size reduces the genetic diversity, and an increase in population size eventually increases the genetic diversity. The exchange of genes between populations inevitably results in greater genetic similarity, while isolation preserves genetic uniqueness. These demographic signatures are passed from generation to generation and that the genomes of present populations reflect their demographic histories. In this aspect, coalescent approaches have been applied in constructing the human demographic histories through the genetic data.

Coalescent theory is a method of connecting gene trees with demographic models. This approach makes it possible to calculate how likely a particular gene tree is under a particular demographic model. It is a retrospective model of population genetics based on the genealogy of gene copies. It uses the mathematical approach for describing the characteristics of the joining of lineages back in time to a common ancestor. The basic idea underlying the coalescent is that, in the absence of selection, sampled lineages can be viewed as randomly 'picking' their parents, as we go back in time (Rosenberg and Nordborg, 2002). Whenever two lineages are traced back to a common ancestor, their lineages coalesce. The coalescent framework was also used to estimate population growth rates and methods for inferring migration rates (Nielsen, 2005). Effective population size (*Ne*) is another important population parameter that helps to explain how human populations evolved and expanded. It is the number of individuals who are contributing the future gene pool. In demographic concept, it can be explained as the number of individuals who are in reproductive age group. It determines the amount of genetic variation for the future generation under the influence of evolutionary factors like genetic drift.

**Epidemiological approach**

The interaction of demography and genetics is more visible in genetic epidemiology. Genetic epidemiology is a branch of science which is concerned with the distribution and evolution of genetic diseases in human populations. It studies the inter relationship between genotype and

phenotype of genetical trait, vis-a-vis environmental factors. Many of the populations went through the demographic events such as bottlenecks, splits and admixtures (Weiss, 1993), after a major expansion at around 50-100 thousand years ago (Relethford, 2001). It resulted in uneven distribution of genetic disorders in different human populations (Polanski and Kimmel, 2003). Genetic epidemiology has demonstrated that genetic variation in human does not fit the simple Mendelian model of diseases associated with a small number of genes each with few alleles (Weiss, 1996).

Genomic epidemiology shows that many Mendelian diseases are concentrated in some, usually small, social or ethnic groups, especially for the rarer diseases. It is because of the limited number of potential mates which further leads to consanguineous marriages and high inbreeding among the population group. Populations that are highly inbred might be subject to inbreeding depression because higher homozygosity unmasks deleterious mutations. Genetic load results from the fixation of slightly deleterious mutations/alleles. Long time small population size will lead to low risk of inbreeding depression but high genetic load. Genetic load of a population is defined as the proportion by which the population fitness is decreased in comparison with an optimum genotype. In other words, it is a measure of the total genotypic selection intensity.

Genomic insight has enhanced our knowledge of Mendelian diseases, and of individual responses to drugs that may be available for a specific disease too. The demographic history of a population may help to predict which groups are likely to show more genetic similarity in their disease patterns. Such population groups can be grouped together for supplying any population specific drugs or chemicals for control and maintenance of the disorder in the population group level, through pharmaco-genomic approach. Genetic variation across population groups has major implications for identifying genes that might be useful for demographic research in epidemiological studies. For population comparisons, the relevant index is the sum of the frequencies of all the deleterious mutations. It is reasonable to assume that mutation occurs with similar frequency in all populations and selection keeps the risky allele under check in some populations. Differences in the gene frequencies of the supposed to be candidate or risk gene for complex disorders indicate that the gene-environment interaction has played an important role.

In recent years, the complex disorders have become the major threat to human health further enhancing the mortality of the individuals. The major problem with the complex disorders is that they are due to polygenic interaction and also because of the gene-environment interactions. In simpler words, not a single gene is responsible for the severity and development of complex disorders like heart disease, diabetes, hypertension, etc, which is again shaped by the life style and food habits. Genetic epidemiology has developed most of the tools necessary for identifying the

genes associated with common complex diseases. Environmental factors including the food habits, lifestyle, occupation, etc., also play important roles in the expression of such disorders. In addition to these, social norm like mating pattern also contribute to the extent of such disorders. Since each population group is characterized by certain mating patterns, especially in India where marriage outside the community (caste/tribe) is not encouraged, the risks of the disorders is maintained and restricted to the population group and carried forward. To deal with these issues – gene-gene interaction and gene-environment interaction in complex diseases, demographic multistate model has become an important tool for sorting out (Ewbank, 2001). It involves analysis and projection of populations stratified by age, sex, and one or several attributes, e.g. health status, region of residence, employment status, household status, etc. It is stochastic process, which at any time occupies one of a set of discrete states (Hougaard, 1999). Human oriented biological research has opened up new vistas for the revelation of the inheritance in man and the continuously evolving interactions in the man versus environment relationships (Pap, 2000).

The concept of *demogenes* has been increasingly applied in genetic epidemiological studies (Ewbank, 2001). These genes have a sufficiently large impact that their effects are important at the population level. Demogenes are those that: i) are associated with the most common diseases, causes of death, or other variables of interest to demographers; ii) have common polymorphisms associated with substantial variation in risk; iii) have large variations in allele frequencies across populations; and iv) interact with environmental or behavioral characteristics being studied by demographers. Such genes are of importance for understanding the gene-environment interaction in the expression of the complex disease in the populations. APOE is one of the demogenes Demographic research on mortality would be significantly altered if genetic epidemiologists discover more such genes which have impact on mortality. The number of demogenes discovered in future will determine how much impact genetics has on demography.

Under suitable assumptions, all individuals with a given disease mutation can be considered a growing subpopulation originating from the individual in whom the original disease mutation occurred. This observation helps in developing methods mapping disease genes (Kaplan et al, 1995; Pankratz, 1998). As the human genome's sequence is more fully understood, this knowledge will provide researchers the basis for identifying variations in gene sequences that influence an individual's susceptibility to the toxic effects of environmental chemicals.

Meitei, S. Y., Saraswathy, K. N., & Sachdeva, M. P. (2012). Demogenetic study – A holistic approach for studying population structure. *International Journal of Human Sciences* [Online]. (9)2, 392- 404.

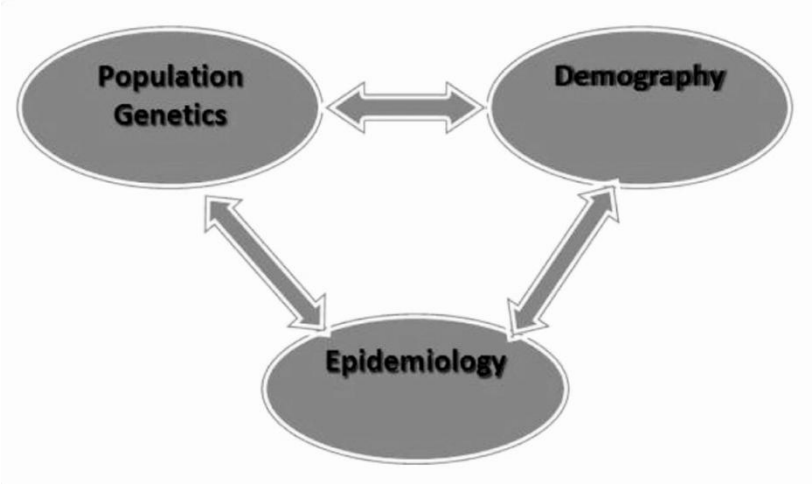


Figure 1: Diagram showing the interrelationship between the population genetics, demography and Epidemiology – the three approaches for understanding the human population structure

Citing the work of Meitei (2011) among the Rongmei tribe of Manipur state (North East India), the demogenetic study reveals a demographically changing population structure, which in turn may influence the evolutionary fate of the population by altering population gene pool. Genetically, the studied population, who are mythologically claimed to be migrated from South West China, reveals a closer genetic similarity with the Chinese and East Asian populations which are morphologically similar too. At the same time, the population is expected to alter its gene pool in the coming generations as the population is experiencing cross marital alliance with the neighboring populations. The changing demographic aspects may transform the population's gene pool, which in turn could switch on/off the clinically important risk alleles (genes) and thereby affecting the community health with complex disorders.

**Conclusion**

In summarizing, we can say that though demography and genetics have moved in different directions, they seek to explain the human dynamics in time and space. The evolutionary fate of a population group basically depends on two parameters – birth and death. The relationship between these two events and human population sizes is the concern of demographers, while population geneticists attempt to quantify the factors responsible for these phenomena and interpret those (Stearns, 1992). Fitting mathematical models to genetic data has helped in verifying, confirming or questioning hypotheses concerning to demographic scenarios or proposing new explanations of the data. With the aid of demography and anthropology, geneticists would finally be able to establish the parameters to determine the expression of genetic variability in human population, beyond the mathematical ideal of random mating (Ramsden, 2008).

It also further provides the way for designing the genetic diseases studies through the demographic or health data. The patterns of genetic variation shed light on recombination, demography, admixture, and evolutionary selection in the human population. The understanding of these patterns of common genetic variation has become a major focus for the large scale clinical association studies as population heterogeneity based on population structure and admixture, leads to spurious associations. Population stratification is also regarded as one of the factors for false association in case-control studies. To put an end to getting such erroneous associations, a good knowledge of population genetics or population structure is much needed. In conclusion, the combination of these two approaches would give a holistic view of any population group. Knowledge of population dynamics in view of demogenetic approach can throw light on the population size and composition through fertility and mortality which in turn measures the selection intensity in the community, thereby further explaining the evolutionary outcome of the community as well the maintenance of any disease in the group.

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