Man In India, 94 (4) : 631-656

THE ROLE OF ANTHROPOLOGICAL GENOMICS AND ECOLOGY IN MEETING THE CHALLENGES OF COMMUNITY HEALTH

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Rise of disciplines like ecology and population genetics in the first quarter of the 20th century revolutionized the field of anthropology and this phase continued from 1930-1980. In this phase, emphasis shifted from the typological approach to the study of human biological diversity and evolution by focusing on the mechanisms that brought change and emphasized the population as the unit on which evolutionary forces operate. The role of anthropological genetics and ecology in meeting the challenges of community health led to rapid growth in publications on studies related to genetic associations with diseases. The rise of molecular genetic techniques in 1980s brought another revolution and changed the nature of inquiry. Traditional studies on classical anthropological genetics have almost become extinct. Human genome project has revealed that human genome is composed of merely 24,000 individual structural genes. There has been a rapid growth in published genetic association studies. The more recent studies of genome-wide association have revealed disease susceptibility loci for several common diseases. From the year 2001 to 2008, the number of original articles published on human genome epidemiology increased from 2492 (34 on meta-analysis) to 7659 (206 on meta-analysis), and totaling to 38718 (912 on meta-analysis) showing rapid annual increase in number. Mendelian factors, major genes and polygenes have been found to be associated with many infectious- and non-infectious diseases. Just as in the case of any other trait, human physical performance characteristics are also strongly influenced by our genetic inheritance and by gene-environment interactions, for example 80% of variation in arm eccentric flexor strength and grip strength may be genetically determined. With the advent of DNA technologies, genome-wide genotype data for multiple populations and the development of methods for detecting selection using SNP data have elicited many genome-wide scans for evidence of positive selection in human populations. Some such studies have identified loci with spatial signatures of selection, such as extreme levels of differentiation and correlations with environmental variables. The implications of public health genomics issues fall into various realms of human life. There are hosts of ethical, legal, and social issues (ELSI) surrounding availability of genetic information issues. There is a major dilemma of fairness in the use of genetic information by insurers, employers, courts, schools, adoption agencies, and the military, among others.

Anthropological Genetics

Biological Anthropology was established in the 19th century, much prior to the acceptance of Wallace and Darwin's theory of natural selection. Evolutionary theory was accepted by scholars soon after publication of Darwin's Book, 'The Origin of Species' in the year 1859, but natural selection theory was not instantaneously accepted. The emphasis of anthropology before and after expounding of Darwinian Theory in the 19th century was on racialology based on the monogenists' theory

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though many scholars continued to support the polygenists' theory. Rediscovery of Mendelian principles of unitary heredity characteristics led to disbanding of blending inheritance at the dawn of 20th century. Discovery of blood groups, universality of Mendelian principles of heredity and laying the foundations of population biology theory gave new directions to anthropology.

Major turnaround came from the synthesis of various evolutionary theories with the science of genetics especially population genetics which was called the modern synthesis by Julian Huxley (1942). The starting point of this period was Fisher's pathbreaker, 'The Genetical Theory of Natural Selection" (Fisher 1930). This period persisted for half a century, from 1930 to about 1980, molecular genetic techniques changed the nature of inquiry though principles of population genetics remained intact with modification brought by various workers. The modern synthetic evolutionary theory brought about two major advances. It ushered in the "golden age" of population genetics, dominated by the three pioneers, Fisher, Haldane, and Wright. It also led to population genetics and microevolution becoming experimental subjects, led largely by Dobzhansky (Dobzhansky 1937).

All these developments led to the shift in the field of physical anthropology from the typological approach to study human biological diversity and evolution by focusing on the mechanisms that brought change and emphasized the population as the unit on which evolutionary forces operate. To highlight this different approach, Sherwood Washburn coined the term 'new anthropology' in 1950s. According to synthetic theory of evolution and from anthropological genetic perspective, evolution may be defined as changes in allele frequencies over time due to mutation, genetic drift, migration, and natural selection. The role of natural selection and genetic adaptations in humans has held a central place in studies under biological anthropology as well as in disciplines such as human genetics and evolutionary biology. Although these disciplines differ slightly in the questions they address and the approaches they use, they intersect in the field of human population genetics, which uses genetic variation data to learn about the past demographic events and the history of natural selection in human populations.

Human Genome Project and Anthropology

The term genome refers to the haploid set of chromosomes specific to the species, while the genomics is inter alia used for an integrated study of the functions of genes, their regulatory signals, and their interactions with the environment and other genes including molecular characterization of the genetic material, i.e. DNA. Human genome project has revealed that human genome is composed of merely 24,000 individual structural genes, which are inherited to define our species. Besides, there are functional polymorphisms within each of these genes. The combinations of such gene variants (haplotypes)/genotypes define us as individuals. Such genetic influences affect our phenotypes that extend across the full spectrum

of human characteristics, whether physical, psychological, or behavioural and also affect our health and disease status. Apart from anthropological genetics, due to molecularization of biological sciences, a term genetic anthropology is also being used for the discipline that combines DNA and physical evidence to reveal the history of ancient human migration. It seeks to answer the questions, "Where did we come from, and how did we get here?"

DNA studies have shown that humans are about 99% identical at the DNA level. But still each individual is unique because of the vast amounts of diversity encountered in the human species. For example, Single Nucleotide Polymorphisms (SNPs) are an abundant source of variation. It is estimated that approximately 10,000,000 such polymorphic sites exist in the human genome. Such variations can be used to infer individual ancestry and population structure. This becomes a central challenge in a variety of different research scenarios and science applications such as the search of susceptibility genes for common disorders, forensics, conservation studies, and population genetics.

In 2006, the National Geographic Society, IBM, geneticist Spencer Wells, and the Waitt Family Foundation launched the Genographic Project, a 5-year nonprofit study that will produce the largest DNA database ever collected for genetic anthropology. The project focuses on obtaining DNA samples from "key populations" composed of people who have lived in a particular region for several generations and maintained the same culture. An estimated 5000 of these so-called key populations live on earth. The project will attempt to choose a subset of these who represent current human genetic diversity. Each person sampled must first give informed consent, and issues such as participants' privacy and the cultural and physical impact of the project are considered. No medical research will be conducted during the study, and no genetic data will be patented. The project's database will be open to the public.

Genomics and Human Races

At the same time, there were anthropologists like Coon who continued to work in the field of racial taxonomies. Despite strong feelings of American anthropologists against the term race, the concept of race could never be banished from anthropological studies. Even today, in most of anthropology departments, paper on race has been a part of their undergraduate and post graduate curricula. When the first draft of human genome project was completed, an editorial in the *New England Journal of Medicine*, emphasizing on the futility of race as a scientific category stated, "Race has become passé" (Schwartz 2001). The methodology behind the Human Genome Project (HGP) presumed human biological commonality declaring that as "the reference" sequence, generating the "genetic terms in which all individuals would be expressed" (M'Charek 2005; Flower & Heath 1993). However, the declaration was proved premature as articles published in major

medical and scientific journals were full of debates about the biological status of race and its usefulness in biomedical research and practice. Genomic and postgenomic studies are giving new lease to the concept of race. But these affirmations have raised many more questions instead of resolving the matter and the critics are debating whether race is dead or alive in the discipline of new genetics.

El-Haj (2007) has explored in his review the relationship between race and the new genetics by considering whether this "race" is the same scientific term as that produced by race science and whether these race-making practices are animated by similar social and political logics. All this shows that the term race has followed the complete circle in the last sixty years. Anthropological genomics investigates the human genomic markers from evolutionary perspective. Genetic methods are now being applied to studies of human-ape divergence, the size and geographic origin of early hominid populations, and the earliest migrations of anatomically modern humans. The field of anthropological genetics uses patterns of genetic similarity among different human populations to infer demographic history, including mating structure, the history of migration and admixture with surrounding groups, and population size fluctuations. New dimensions have been added to field of anthropological genetics with recent technological developments. Ancestry Information Markers (AIMS) is one technology for reading race in the DNA. (It is currently available as a commercial product for forensic and biomedical researchers, among other potential clients). AIMS technology was designed to identify genetic markers that could distinguish one "continental" group from another (Shriver *et al.* 2003, 2005; *http://www.dnaprint.com/welcome/home/ index/php*).

Anthropological Genomics and Human Health

Genomics is the study of the entire human genome. The science of genetics emphasized on the study of the functions and effects of single genes; where as genomics explores not only the actions of single genes, but also the interactions of multiple genes with each other and with the environment. As a result, genomics has great potential for improving the health of the public.

The role of anthropological genetics in meeting the challenges of community health was established in the 19th century itself when foundations of Eugenics were laid though that was later misused on the basis of wrong assumptions and apprehensions. Studies on anthropological genetics over the years have revealed the existence of spatial hot spots of certain diseases attributed to the founder effect and genetic structure of host-pathogen interactions. The rapid growth in published genetic association studies (Hill 2006; Sharma 2007, Sharma *et al.* 2013) and the success of genome-wide association studies (GWAS) in finding disease susceptibility loci for several common diseases (Bellamy 2006) present major challenges for knowledge synthesis and dissemination. Knowledge synthesis is needed to guide further research, drug discovery efforts (Burke *et al.* 2006), and

translational efforts for personalized risk assessment and therapy. The recent trend toward direct-to consumer advertising of whole-genome analysis by several companies underscores the importance of a credible process for data synthesis and evaluation of the validity and utility of claims related to genetic prediction of disease risks (Khoury 1996; Kandun *et al.* 2006). From the year 2001 to 2008, the number of original articles on human genome epidemiology that were published increased from 2492 (34 on meta-analysis) to 7659 (206 on meta-analysis), and totaling to 38718 (912 on meta-analysis) showing that the annual number has been rising rapidly. The applications of human genomics in the field of public health fall in the purview of a new field, called 'Public Health Genomics'. This is visualized as more effective personalized preventive care and disease treatments with better specificity, targeted to the genetic makeup of each patient (see Khoury 1996). This emerging field assesses the impact of genes and their interaction with behaviour, diet, and the environment on the population's health. The promise of public health genomics is to have practitioners and researchers accumulating data on relationships between genetic traits and diseases across populations, to use this information to develop strategies to promote health and prevent disease in populations, and to more precisely target and evaluate population-based interventions. Public health genomics is an exciting, multidisciplinary field that brings all the public health sciences to bear on the emerging challenge of interpreting the significance of genetic variation within populations and applying that knowledge in order to improve the health of the public. A workshop on implications of genomics for public health was conducted Board on Health Promotion and Disease Prevention (HPDP) (see Hernandez 2005).

Spatial Dynamics of Infectious Diseases

It has been a major premise of physical anthropology that natural selection sifts through genomic diversity for adapting to the environments in which humans have been living through ages. Infectious diseases have been acting as an agent of natural selection. The dependence of infectious disease processes on their specific spatial and ecological context has been receiving considerable recent attention. Spatial analysis of infectious disease processes recognizes that host-pathogen interactions occur in specific locations at specific times and that often the nature, direction, intensity and outcome of specific interactions depend upon the specific location and identity of both host and pathogen (Real & McElhany 1996; Hess *et al.* 2001). Real and Biek (2007) have reviewed the manner in which the physical organization of the landscape has been shown to influence the population dynamics and spatial genetic structure of host-pathogen interactions, and how we might incorporate landscape architecture into spatially explicit population models of the infectious disease process to increase our ability to predict patterns of disease occurrence and optimally design vaccination and control policies.

Anthropology reveals that beginning about 10,000 years ago, a major shift occurred in most human populations, from a nomadic hunting and gathering lifestyle to relatively settled and primary food production lifestyle. This shift involved major changes in human social organization, diet, demographics, and behaviour that created conditions favorable for zoonotic infections to make the transition to human hosts, and enabled the preexisting human pathogens to evolve into more virulent forms. Consequently, the first epidemiologic transition with a rise in infectious diseases occurred during this Neolithic Revolution. The concept of the epidemiologic transition was first formulated by Omran as a model for integrating epidemiology with demographic changes in human populations (Omran 1971).The second epidemiologic transition is associated with industrialization that witnessed the shift from infectious to chronic disease mortality. The third epidemiologic transition marks the recent resurgence of infectious disease mortality characterized by newly emerging pathogens and antibiotic resistant pathogens in the context of an accelerated globalization of human disease ecologies (Gubler 1996; Patz *et al.* 1996). The Centers for Disease Control and Prevention (CDC) has compiled a list of 29 newly emerging pathogens since 1973 (Satcher 1995).

Technological innovations in the last 30 years and sampling efforts designed to facilitate genome-wide association mapping, human geneticists are now studying the geography of genetic variation in unprecedented detail. With high genomic coverage and geographic resolution, these studies are identifying loci with spatial signatures of selection, such as Satcher 1995extreme levels of differentiation and correlations with environmental variables. Collectively, patterns at these loci are beginning to provide new insights into the process of human adaptation (Novembre and Di Rienzo 2009).

Spatial analysis of prevalence of some select infectious diseases reveals many hot spots. Tuberculosis (TB) disease has long history. An examination of Egyptian mummies and tissue samples from graves suggest that tuberculosis infections started more than 5,400 years ago, but scientists believe the bacteria is probably three times as old. TB hot spots in 2006 (new and relapse cases) were: India: 1,228,827; China: 940, 889; South Africa: 303,114; Indonesia: 277,589; Pakistan: 176,678. Another major epidemic disease, the bubonic plague has been responsible for more than 200 million deaths in the 14th century, when the "Black Death" was blamed for wiping out nearly a quarter of Europe's population. Today, the World Health Organization says, nearly 3,000 cases of the plague-spread by wild animals and causing painful swollen lymph nodes, or buboes, in the armpit, groin and neck-are still reported every year, mostly in Africa. According to the WHO, five African countries accounted for nearly 99 per cent of the cases of bubonic plague worldwide in 2003. These hot spots were: Democratic Republic of Congo: 1,092 cases; Madagascar: 993 cases; Mozambique: 31 cases, Uganda: 24 cases; Algeria: 11 cases.

Poliomyelitis disease has been almost eradicated from the world through oral vaccination. By 2007, only four countries remained where polio was still prevalent - Afghanistan, India, Nigeria and Pakistan. Consequently, other Asian and African countries are still at risk of reinfection. Yellow fever dates back more than 400 years and can cause epidemics with a fatality rate exceeding 50 per cent in unvaccinated populations. Symptoms of the disease, which is transmitted by mosquitoes, include fever, a slow pulse, muscle pain, a headache, shivers, nausea and vomiting. Outbreaks of yellow fever occurred in Africa, Europe, the Caribbean and Central and North America until the start of the 20th century. The last epidemic of yellow fever in North America was in New Orleans in 1905. Today, the World Health Organization estimates there are 200,000 cases each year, causing 30,000 deaths, predominantly in Africa and South America. The known yellow fever hot spots are: Ivory Coast; Peru; Colombia; Paraguay; Bolivia.

Genetic Susceptibility to Diseases

Race and Disease Prevalence

As discussed earlier, with the molecularization of the life sciences, the molecularization of race has also taken place. In contrast with the practices that characterized a phenotypically based race science, establishing the correlation of disease risk and racial difference in today's molecular biological laboratories involves "reading race in the DNA" (Fullwiley 2008) and, in turn, it involves classifying DNA "ethnoracially" (M'Charek 2005; Montoya 2007). The logic of reading race via that molecular optic in the contemporary research practices of postgenomic medicine diverges from that which guided either the typological thinking of race scientists or the molecular logic of diagnosing blackness via sickle-cell disease earlier in the twentieth century.

In the first half of the 20th century, sickle-cell disease was understood to be prevalent amongst blacks (or Negro). Later on it was reported from India and Mediterranean counties. Molecular studies have shown that Indian and African mutations in the haemoglobin gene are independent of each other (see Sharma *et al.* 2002). Montoya (2007) has shown that racial categories have shifted or proliferated over time in the United States as a result of migrations and hybridization, although the primary divisions between white, black, Asian, and Native American persist. When risk for asthma in the Puerto Rican population was analyzed in terms of ancestral populations believed to have either a "harmful (exacerbating) or helpful (mitigating) effect on asthma severity as well as on frontline drug response" (Fullwiley 2008). A research project on prevalence of diabetes among Mexican Americans has revealed that there is strong evidence that Mexican Americans living in the barrio have considerably more Native Amerindian genetic admixture and as a result may have higher genetic susceptibility to diabetes (Montoya 2007).

Keppel *et al.* (2002) examined data between 1990 and 1998 on a set of ten health status indicators relevant to the Healthy People 2010 goals. These indicators included a range of health conditions (coronary heart disease, cancer, tuberculosis) as well as indicators with more direct social referents such as live births to teenagers ages 15–17 and suicide and homicide rates. These indicators were examined in relation to racial and ethnic categories employed in the U.S. Census: non-Hispanic white; non-Hispanic black; Hispanic; American Indian or Alaska Native; and Asian or Pacific Islander. They found that for mortality related to disease and traumatic injury, rates declined for all population subgroups between 1990 and 1998. With respect to racial and ethnic disparities, black Americans' rates for six measures (total mortality, heart disease, lung cancer, breast cancer, stroke, and homicide) exceeded other groups' rates by a factor ranging from 2.5 to almost 10 during both time periods. Other ethnic groups had higher rates for suicide (white Americans) and motor vehicle accidents (American Indian and Alaskan Natives). Overall, Asians and Pacific Islanders tended to have the lowest mortality rates, although Hispanics were lowest for strokes.

The racial disparities in health conditions can be explained with the help of many models. From the literature review, Dressler (1993) identified four general models: a racial-genetic model; a health-behavior model; a socioeconomic status model; and a social structural model. There are large differences in rates of low birth weight (defined as birth weight less than 2500 grams) and rates of hypertension (blood pressure higher than 140 mm Hg systolic and/or 90 mm Hg diastolic) between black and white Americans. Literature reviews showed that prevalence rates were extremely variable across populations in Africa and people of African descent in the New World. Studies have demonstrated an east-west gradient in hypertension prevalence: West African samples had the lowest (16%) prevalence, West Indian populations had an intermediate (26%) prevalence, and African American populations had the highest (33%) prevalence (Cooper *et al.* 1997). Grim & Robinson (1996) tried to explain blood pressure disparities in the form of Grim's "slavery hypothesis". According to this hypothesis, a salt-sparing genetic variant was selected for in Africa (a kind of "thrifty genotype") owing to chronic salt shortages. Efforts made to identify genetic variants for a racial-genetic component in blood pressure have not been particularly successful (Crews & Williams 1999, Oparil et al. 2003); and those candidate genes that do appear to be associated with blood pressure are not differentially distributed across conventional racial groups (Daniel & Rotimi 2003), nor do they differ between African Americans and first-generation African immigrants (Bouzekri et al. 2004). Absence of associated genetic variant for some physiological phenotypic variability does not mean, such associations are absent for all health related traits. However, Adeyemo *et al.* (2005) have localized genetic on blood pressure in chromosome 6 and 7.

The racial health disparities can be explained on the basis of principles of population genetics, cultural inheritance and environmental correlates. For example, population genetics theory tells us that natural populations of living organisms often have complex histories consisting of phases of expansion and decline, and the migratory patterns within them may fluctuate over space and time. When parts of a population become relatively isolated, e.g., due to geographical barriers, stochastic forces reshape certain DNA characteristics of the individuals over generations such that they reflect the restricted migration and mating/reproduction patterns. Such populations are typically termed as genetically structured and they may be statistically represented in terms of several clusters between which DNA variations differ clearly from each other (Corander et al. 2008). Prevalence of diseases in them can be explained in terms of their genetic structure and environmental correlates.

Ethnic Groups, Pharmacogenetics and Genomics

Pharmacogenetics is the study of how genes influence an individual's response to drugs. It is of interest anthropologically when we individual differences to drug response among cohorts/human populations. Similarly, pharmacogenomics can be defined as the study of DNA sequence variation as it relates to differential drug response in individuals. Pharmacogenetic research has gained enormous momentum, with recent advances in molecular genetics and genome sequencing. For example, cytochrome P450 3A enzymes (CYP3A) play a major role in the metabolism of steroid hormones, drugs and other chemicals, including many carcinogens. The individually variable CYP3A expression, which remains mostly unexplained, has been suggested to affect clinical phenotypes. Schirmer *et al. (2006)* investigated the CYP3A locus in five ethnic groups. The degree of linkage disequilibrium (LD) differed among ethnic groups, but the most common alleles of the conserved LD regions were remarkably similar. Non-African haplotypes were few; for example, only four haplotypes account for 80% of common European Caucasian alleles. They further concluded that their data were consistent with a functional relevance of CYP3A4*1B and with selection against this allele in non-African populations. The elimination of CYP3A4*1B involved different parts of the CYP3A locus in European Caucasians and Asians. Because CYP3A4 is involved in the vitamin D metabolism, rickets may have been the underlying selecting factor.

Genetic Susceptibility to Infectious Diseases

It is now established that susceptibility to diseases depends on interactions among environment, disease vectors and host's genetic factors. An exposure to a microbial agent is obviously required for infection and disease to occur. There are people in the medical profession who profess that infectious diseases are

purely environmental diseases. However, epidemiological evidence has accumulated since the 1930s that human genetic factors play a particularly important role in immunodeficiency and susceptibility to infectious diseases. Genetically determined resistance or susceptibility to an infectious agent is the mirror image of each other. The term resistance typically applies when persons infected by disease causing microbe strains do not develop disease. It is more common to talk of the susceptibility of the patients rather than resistance to a disease.

Genes, Gene Polymorphism and Disease Susceptibility: Association Studies

Malaria has been major cause of mortality in the tropics in the past even at present too, resulting in the death of millions of people. The classical genetic marker that has been extensively cited as an example of genetic adaptation in environs where malaria was endemic is the classic sickle hemoglobin variant against the severe forms of malaria caused by *Plasmodium falciparum* (Allison 1954). The hetrozygote-superiority has been extensively confirmed in case-control studies over the years. There are many other well known examples include the association of Duffy blood group negativity with resistance to *Plasmodium vivax* malaria; ABH non-secretors, due to homozygosity for a FUT2 gene, being resistant to diarrhea caused by Norwalk virus, a norovirus; the association of blood group O with cholera severity. Certain base pair deletions in different genes are known to provide resistance against HIV-1 infection and malaria. Mendelian inborn errors of immunity associated with multiple infections, often referred to as conventional primary immunodeficiencies (PIDs), have since been reported (Ochs et al. 2006). Similarly there are hotspots of leprosy. Gene mapping technique and detailed within-family association analysis led to the mapping of the relevant chromosome 10p13 susceptibility gene to exon 7 of the macrophage mannose receptor for leprosy (Siddiqui *et al.* 2001).

The field of the human genetics of infectious diseases entered the molecular and cellular era in the early 1950s, with a series of landmark discoveries. There are now definitive evidence that genetic factors of host play a major role in determining differential susceptibility to many infectious diseases of humans, such as malaria, HIV/AIDS, tuberculosis, and invasive pneumococcal disease. The identification of the relevant genetic loci has come from a variety of approaches. Case-control studies assessing biologically plausible candidate genes have provided most convincing evidences in identifying the relevant loci. There are about 25 gene-infectious disease associations in humans that have been replicated with reasonably convincing evidence of association of a specific allele with disease (Hill 2006; Alcaïs *et al.* 2009). The list of human infectious diseases and the genetic associations are presented in Table 1.

TABLE 1: GENETIC LOCI ASSOCIATED WITH SUSCEPTIBILITY TO HUMAN INFECTIOUS DISEASES

Disease / Pathogen	*Genetic locus*
Malaria	alpha-globin, beta-globin, G6PD, SLC4A1, MAL/TIRAP, DARC
Tuberculosis	HLA-DR, INF-γ, SLC11A1, VDR, MAL/TIRAP, CCL2, CR1
HIV/AIDS	HLA-B, CCR5, CCR2, RANTES
Bacteremia	MBL2, PTPN22, CD32, MAL/TIRAP
Leprosy	HLA-DR, PARK2/PACRG
Norovirus diarrhea	FUT2
Prion diseases	PRPN
Cholera	ABO blood group

Mendelian Predisposition to Diseases

A number of disorders (see Table 2) are known to have Mendelian predisposition/ resistance to specific infections (Picard et al.2006). Individuals carrying the common wild-type alleles are inherently susceptible to the particular pathogens, whereas individuals carrying the mutant alleles display almost complete and apparently specific protection against these pathogens. Protection against *Plasmodium vivax,* a pathogen that causes malaria, is conferred by a lack of Duffy blood group, chemokine receptor (DARC), a coreceptor for *P. vivax*, on erythrocytes (Miller *et al.* 1976).

TABLE 2: MENDELIAN PREDISPOSITION/RESISTANCE TO SPECIFIC INFECTIONS

Infectious Agent	*Phenotype*	*Clinical/Immunological phenotype*	*Gene*
P. vivax	NR	Lack of coreceptor	*DARC*
HIV-1	NR	Lack of coreceptor	*CCR5*
Norovirus	NR	Lack of coreceptor	*FUT2*
Parvovirus	NR	Lack of coreceptor	?
Neisseria	Inv. Disease	MAC deficiency	*C5*, *C6*, *C7*, *C8A*, *C8B*, *C8G*, *C9*
	Inv. disease	Properdin deficiency	*PFC*
Mycobacteria	MSMD	IL-12/ IL-23–IFN-γ defic.	*IFNGR1*, *IFNGR2*, *STAT1*, *NEMO*, *IL12B*
	Disseminated tuberculosis		*IL12RB1*
Streptococcus Pneumoniae	Inv. disease	IRAK-4 and MyD88 deficiency	*IRAK4*, *MYD88*
EBV	X-linked lympho- proliferative disease	SAP and XIAP def.	*SAP*, *XIAP*
HPV	Epidermodysplasia verruciformis	EVER1/EVER2 deficiency	*EVER1*, *EVER2*
HSV-1	Encephalitis	Impaired production of antiviral IFNs	*UNC93B*, *TLR3*
Trypanosoma Evansi	Febrile episodes	No trypanolytic activity	*APOL1*

NR, Natural resistance; C, complement component; MAC, membrane attack complex; NEMO, NF-?B essential modulator; PFC, properdin factor, complement.

Major Gene Concept

Since the discovery that susceptibility to diseases was dependent on many factors, the concept of major gene evolved in 1960s (Edward 1969). A major gene has lower penetrance than a Mendelian due to a greater influence of other genes and environmental factors of an individual. This concept was first formalized when many diseases and disorders were found to run in families and statistical methods were developed and used like complex segregation analysis, based on a model of inheritance in which a given phenotype may result from the joint effects of a major locus, a polygenic component, and environmental factors (Lalouel *et al.* 1983, Khoury *et al.* 1993). Since the development of these statistical methods, several major genes have been identified by segregation analyses in a number of complex traits, including infectious disease-related phenotypes in leprosy, malaria, schistosomiasis, and some viral infections (Casanova and Abel 2007).

Foreign Latent Genomes and Infectious Diseases

The field of genomics takes into account the entire genome of an organism and not just its individual genes. The studies have shown that viral DNA at times integrates with host's chromosome and replicates there. Such integrations are seen for many viral diseases. The studies done on experimental animals have shown that showed that mice with a latent infection of a Herpes virus were less susceptible to bacterial infections.

Genetic Susceptibility to Non-infectious Diseases

Human Genome Epidemiology Network (HuGENet) is an informal global collaboration of individuals and organizations interested in accelerating the development of the knowledge base on genetic variation and human health (Khoury and Dorman 1998) (*http://www.cdc.gov/genomics/hugenet/ default.htm*). Associations of diseases with genetic variation reported in the literature are being reassessed to study the repeatability of the results. Consequently Pilot studies were planned in selected fields to assess cumulative evidence on gene-disease associations, calibrate the proposed guidelines, and integrate the findings into comprehensive field synopses. Pilot field synopses have been conducted for several diseases. Many associations in the Alzheimer's disease, schizophrenia, and 2 cancer-related field synopses have yielded formally statistically significant results at the $P < 0.05$ level (Khoury *et al.* 2009).

Gene Therapy

Gene therapy may be used for fixing genetic defects, but it is still in a topic of reaseach than being factually commonly used approach. Even in the United States of America, the Food and Drug Administration (FDA) has not yet approved any human gene therapy product for sale. The experiments done in gene therapy have

not proved very successful in clinical trials. Little progress has been made since the first gene therapy clinical trial began in 1990. In 1999, gene therapy suffered a major setback with the death of 18-year-old Jesse Gelsinger. Jesse was participating in a gene therapy trial for ornithine transcarboxylase deficiency (OTCD). He died from multiple organ failures 4 days after starting the treatment. His death is believed to have been triggered by a severe immune response to the adenovirus carrier. Another major blow came in January 2003, when the FDA placed a temporary halt on all gene therapy trials using retroviral vectors in blood stem cells. FDA took this action after it learned that a second child treated in a French gene therapy trial had developed a leukemia-like condition. Both this child and another who had developed a similar condition in August 2002 had been successfully treated by gene therapy for X-linked severe combined immunodeficiency disease (X-SCID), also known as "bubble baby syndrome."

There are some recently reported examples of gene therapy, but these have been done on experimental animals by using nanotechnology to treat torpedo cancer. Some cases of treatment of blindness have also been done humans.

Nutrition and Health

Nutrigenomics

Nutrition is an important determinant of health. The field nutrigenomics states that all the substrates that are ingested as food affect the genome of an individual. This may be in tune with traditional Indian wisdom of '*tamsik*-' and '*satwik*-' food, wherein the former generates what is perceived as bad deeds while the latter generates good deeds. This may be achieved by up- and down-regulating the genes triggered by food substrates. An example of the role of nutrition would be the methylation pathway involving methylene tetrahydrofolate reductase (MTHFR). An individual with the gene variant or SNP (single nucleotide polymorphism) may need increased intake of B12 and Folinic acid to override the effect of a variant SNP. Increased risks for neural tube defects and elevated homocysteine levels have been associated with the MTHFR C677T polymorphism.

The ability to taste PTC/PROP has been extensively studied in human populations across continents and several anthropological significant trends have been noted. The ability to taste PTC has long been debated to have protective value in rejecting bitter poisonous substances (see Sharma 2005). PTC/PROP are chemically related to the isothiocyanates and goitrins, which are naturally present in cruciferous vegetables such as cabbage, broccoli, Brussel sprouts, turnips, kale, cauliflower, mustard green (see Drewnowski and Gomez-Carneros, 2000). PTC tasters would tend to eat such raw vegetables in fewer amounts. Then how to explain the existence of a mutant nontaster allele in significant proportions in many populations of the world? The persistence o PTC nontaster genotype has been

explained by the advantage it provides in certain specific environmental conditions. Thimmulappa *et al.* (2002) have identified the blueprint of genes and enzymes in the body that enable sulforaphane, a compound found in broccoli and other vegetables, to prevent cancer and remove toxins from cells. Lampe and Peterson (2002) have investigated the role of cruciferous vegetables (e.g., broccoli, Brussels sprouts) having chemo-protective effect and the study outlines the metabolism and mechanisms of action of cruciferous vegetable constituents, on biotransformation systems and summarizes the epidemiologic and experimental evidence for an effect of genetic polymorphisms (genetic variations) in these enzymes on response to cruciferous vegetable intake. Implications of PTC bitter taste receptor gene polymorphism in human health and disease have been discussed in detail by Sharma (2008). PTC locus has also beeknown to have implications in human physique and body composition (Sharma and Chaudhary 2013; Sharma and Kaur 2014).

Diabetes mellitus is a disease affecting millions of people across the globe. It has been usually believed that the transition to a Western lifestyle and diet results in major prevalence increases of type 2 diabetes (Weiss *et al.* 1984; Szathmary 1990, 1994), though it is unclear whether this is also true for the transition from hunting gathering to agriculture. It is usually cited in anthropological literature that according to thrifty genotype hypothesis proposed by Neel (1962), the variants that increase risk to type 2 diabetes and obesity may be at high frequency in human populations when humans were hunter and gatherers. He reasoned that because ancestral populations underwent seasonal cycles of feast and famine, they would have benefited from having extremely efficient fat and carbohydrate storage. When food production and storage, as a result of first cultural revolutions during Neolithic, resulted in more reliable food availability, this ancestral thriftiness became detrimental, and in contemporary populations, it contributes to the increased prevalence of diabetes and obesity due to high carbohydrate light and with no scarcity of foods, these being in plenty and sedentary life style. Consistent with the notion that thriftiness is an ancestral state, many alleles that increase risk to type 2 diabetes and other metabolic disorders are ancestral (i.e., shared with chimpanzee), whereas the alternative alleles at those polymorphic sites protect against the disease (Di Rienzo & Hudson 2005).

In a revision of the original thrifty genotype hypothesis, Neel (1999) proposed that the changes that accompanied the spread of agriculture, including the reduction in dietary diversity and increased intake of a diet composed mainly of carbohydrates, represented an important step in the shift to overall environmental conditions that favour the development of type 2 diabetes in individuals carrying the thrifty genotype. However, it has been debated whether food availability and reliability were indeed higher in agriculturalists compared with foragers (Cohen & Armelagos 1984, Larsen 2003, Benyshek and Watson 2006. It has been further argued that as

a consequence of the thrifty genotype hypothesis, populations with secure access to food resources may have evolved adaptations that slowed the insulin response and decreased the storage of energy as fat, thus resulting in a decrease in type-2 diabetes prevalence over time. Diamond (2003) proposed that the low prevalence of type-2 diabetes in Europeans reflects a longer history of stable food supply in these populations. As an extension of the argument, it will follow from it that populations that have now higher prevalence of type-2 diabetes, never had steady food supply in the past. India now has the largest number of such patients than anywhere else in the world. The latter hypothesis can be raised. Under this scenario, alleles that protect against type-2 diabetes are expected to have increased in frequency and to carry a signature of positive selection (e.g., be associated with high EHH). It is important to note that changes of allele frequencies, even if driven by strong positive selection, take at least hundreds of generations.

Paradies *et al.* (2007) while examining the thrifty genotype hypothesis (THG) conclude that although there are compelling reasons to regard the high prevalence of type 2 diabetes mellitus as a by product of our biological incapacity to cope with modern affluent and sedentary lifestyles, there is at present no consistent evidence to suggest that minority populations are especially genetically susceptible. They further argue that it is not clear why such genetic differences would be expected, given the original pan-species orientation of the TGH. According to them, the limitations inherent in current applications of the TGH demonstrate that genetic research into complex disease demands careful attention to key environmental, social, and genetic risk factors operating within and between groups, not the simplistic attribution of between-group differences to racialized genetics.

A competing hypothesis to Neel's (1962) thrifty genotype model, was proposed by Hales & Barker (1992), who gave 'thrift phenotype hypothesis', according to which individuals born small (defined as less than 2500 g) who gain excess weight as older children or adults are at elevated risk for developing metabolic risk factors for hypertension, diabetes, and high cholesterol. They argued that the fetal response to prenatal undernutrition induces a "thrifty phenotype" characterized by insulin resistance, a shift in circulation to protect the brain ("brain sparing"), and a nutrient-conserving reduction in organ growth. They further argued that these adjustments enhance immediate fetal survival but subsequently increase the risk of developing diabetes and cardiovascular disease (CVD) in the event that the individual later experiences nutritional excess and weight gain. This model proposed that high rates of diabetes among some populations might trace to stressful intrauterine environments rather than to susceptibility alleles (see Kuzawa and Quinn 2009). As an extension of the thrifty phenotype model, Bateson (2001) suggested that fetal adjustments to prenatal nutrition are not merely designed to improve immediate survival, but also are initiated in anticipation of nutritional conditions during childhood.

Sladek *et al.* (2007) conducted genome-wide scans for associations with Type 2 diabetes mellitus and tested 392,935 single-nucleotide polymorphisms in a French case–control cohort. Markers with the most significant difference in genotype frequencies between cases of type 2 diabetes and controls were fast-tracked by them for testing in a second cohort. On the basis these analyses, Sladek et al. (2007) have concluded that the disease results from the interaction of environmental factors with a combination of genetic variants, most of which were hitherto unknown. They, however, identified four loci containing variants that confer type 2 diabetes risk, in addition to confirming the known association with the TCF7L2 gene. These loci include a non-synonymous polymorphism in the zinc transporter SLC30A8, which is expressed exclusively in insulin-producing b-cells, and two linkage disequilibrium blocks that contain genes potentially involved in b-cell development or function (IDE–KIF11–HHEX and EXT2–ALX4). These associations explain a substantial portion of disease risk and constitute proof of principle for the genome-wide approach to the elucidation of complex genetic traits.

Lactase persistence is the production, after infancy/babyhood, of the enzyme lactase, which breaks down the milk sugar lactose into glucose and galactose so that it can be further processed in the intestines. This condition is uncommon in nonhuman species. In some human populations lactase persistence is relatively common. Prevalence of lactase persistence varies greatly among human populations and has been shown to co-occur with cultural traits that involve the inclusion of dairy products in the diet. A cline in the lactase persistence phenotype exists within Europe such that persistence is highest among populations in the Northwest and lowest among those in the Southeast (see Swallow 2003). Similar clinal pattern is seen in pastoral populations of the Middle East (e.g., Bedouin) and sub-Saharan Africa (e.g., Fulani and Tutsi).These findings led to the hypothesis that alleles causing lactase persistence were advantageous when populations adopted dairy farming and shifted to a diet in which milk is a major adult staple (McCracken 1971, Simoons 1970, Kretchmer 1972).

In Europeans, lactase persistence has been shown to be due to a polymorphism about 14 kb upstream of the gene coding for the lactase enzyme (*LCT*). This polymorphism, denoted C/T–13910, has been reported to affect lactase reduction via changes in transcription levels and the genomic region containing this polymorphism has been investigated for signatures of positive natural selection in ethnically diverse population samples, with a special focus on the haplotype associated with persistence in Europeans (Bersaglieri *et al.* 2004). Consistent with the idea that lactase persistence was advantageous in European populations, multiple polymorphisms displayed unusually large differences in allele frequencies between Caucasoid and non- Caucasoid populations, and the haplotype structure exhibited extremely high EHH in European populations. The time since expansion of the

C/T–13910 variant in Europeans was estimated to be 2188–20650 years, roughly consistent with the likely time of onset of dairy farming. The above findings were bolstered by genome-wide scans for selection, which showed that the *LCT* gene in Europeans contains the strongest signal of a partial selective sweep in the human genome (Consortium 2005, Sabeti *et al.* 2007, Voight *et al.* 2006 and Williamson *et al.* 2007). Although it is common in Europeans, the C/T–13910 variant is absent or very rare in some African and Middle Eastern populations where lactase persistence is high, which led to the hypothesis that different variants underlie the lactase persistence phenotype across populations. Indeed, genotype-phenotype association studies in African pastoral populations found that several polymorphisms near the C/T–13910 (G/T–14010, T/G–13915, and C/G–13907) may cause lactase persistence. These SNPs originated on different haplotype backgrounds from the European C/T-13910 SNP and from each other. Genotyping across a 3-Mb region demonstrated haplotype homozygosity extending >2.0 Mb on chromosomes carrying C-14010, was found consistent with a selective sweep over the past ~7,000 years (Tishkoff *et al.* 2007).

Alcohol Dependence, Ethanol Response and Ethanol-Related Traits

Alcoholism is one of the most common and costly health problems in the whole of the world. There are correlations between acute behavioral responses to ethanol and ethanol consumption or incidence of alcoholism in both animals and humans (Davies *et al.* 2004). In humans, alcoholism (alcohol dependence) is a common, genetically influenced complex disorder across the world. Family, twin and adoption studies demonstrated that genetic factors play a strong role in the etiology of alcoholism, accounting for 50–60% of the population variance in both men and women (Mayfield *et al.* 2008, Prescott *et al.* 2006). Although genetic factors are important, alcoholism is a complex disease with environmental influences. Further, the architecture likely involves many genes with small effects along with environmental influences, as well as potential interactions between them. Therefore, it is a challenge to explore the molecular mechanisms underlying the genetic propensity to excessive alcohol consumption and use these for the development of new treatments for alcoholism. Many experimental strategies [linkage scan, association study, quantitative trait loci (QTLs) and microarray gene expression] have been applied in the studies of alcoholism and ethanol response in order to identify genes or chromosomal regions in both humans and model organisms (Dick and Foroud 2003; Schumann *et al.* 2003).

Alcohol dehydrogenase genes in the *ADH1*cluster play an important role in ethanol metabolism, harbor variation associated with susceptibility to alcoholism. This includes a nonsynonymous polymorphism (R47H) in the *ADH1B* gene, which has near-fixation frequency in Asian populations and is rare elsewhere (Osier *et al.* 2002a,b). Voight *et al.* (2006) found evidence for selection at the *ADH1* gene

cluster on the basis of strong EHH in East Asian populations (Voight *et al.* 2006). These results strongly argue for a selective advantage conferred by the *ADH1* polymorphism(s). However, whereas *ADH1* polymorphisms clearly affect variation in the processing of a common dietary component, i.e., ethanol, it is unclear whether ethanol consumption itself was the selective pressure underlying the observed population genetic pattern. Because the high-activity *ADH1* alleles result in an accumulation of acetaldehyde in response to alcohol load and because acetaldehyde has antiprotozoal activity, Goldman & Enoch (1990) proposed that these alleles are selectively advantageous because they protect against severe infectious diseases by protozoans. Other specific dietary components may also be important. For example, two genome scans found evidence for selection from EHH for genes important in vitamin transporter activity and cofactor transporter activity (Tang *et al.* 2007, Voight *et al.* 2006). In addition, Wang *et al.* (2006) found signatures of positive selection for several genes involved in protein metabolism (*ADAMTS19-20*, *APEH*, *PLAU*, *HDAC8*, *UBR1*, and *USP26*) and a significant excess of signals in the group of genes in this biological category compared with other groups.

Genetic Variation and Human Performance

Just as in the case of any other trait, human physical performance characteristics are also strongly influenced by our genetic inheritance and by gene-environment interactions, for example 80% of variation in arm eccentric flexor strength and grip strength may be genetically determined (Montgomery and Safari 2007). From race and performance perspective, it has been seen that best runners in the Olympics have always been from the Black race, while best discuss throwers belonged to white race. How to explain such findings? A number of studies have been undertaken to quantify the scale of the genetic contribution to sporting phenotypes (such as run times), or what may called intermediate phenotypes that likely to influence global athletic performance (these have been reviewed by Montgomery and Safari 2007). These intermediate phenotypes might be anatomical (bone mineral density, muscle mass), physiological (anaerobic threshold), biochemical (van Rossum *et al.* 2004), or even behavioral (desire to exercise, pain tolerance). In general, heritability seems every bit as high as for other human traits. Thus, heritability of human left ventricular mass (LVM) may be as high as 0.69 (Swan *et al.* 2003). It has been calculated that genetic factors account for up to 80%of the variance in human skeletal muscle mass in the young (Seeman *et al.* 1996). Similarly muscle function is also strongly genetically influenced (Bouchard & Malina 1983, Beunen and Thomis 2004), although it is also strongly influenced by gene-environment interaction (Tiainen *et al.* 2005). Heritability studies have shown that up to 82% of variation in arm eccentric flexor strength, grip strength, and pull and push strength may be genetically determined (Thomis *et al.* 1998; Beunen and Thomis 2004).

Ethical, Legal and Social Issues

The potential implications of the Human Genome Project (HGP) are vast in health and disease. Public health genomics issues fall into various realms of human activities. There are benefits and controversies which need to be addressed. On implications of the genomic information being increasingly offered as courtroom evidence, Abrahamson (1999) said, "DNA technology is becoming increasingly integrated into our judicial system, especially in the criminal justice system. DNA analysis has proved to be a powerful tool to identify perpetrators and to exonerate the innocent. The assimilation of DNA technology into criminal trials comes just as the role of the judiciary as gatekeeper in assessing scientific evidence is changing." There are hosts of ethical, legal, and social issues (ELSI) surround availability of genetic information issues. There is a major dilemma of fairness in the use of genetic information by insurers, employers, courts, schools, adoption agencies, and the military, among others. Discrimination cases based on the dissemination of genetic testing information to official or private entities will become commonplace (see Sharma, 2007; where some hard evidences on many such issues have been highlighted).

There are clinical issues like the education of doctors and other health service providers, patients, and the general public in genetic capabilities, scientific limitations, and social risks; and implementation of standards and quality-control measures in testing procedures. There are reproductive issues like adequate informed consent for complex and potentially controversial procedures, use of genetic information in reproductive decision making, and reproductive rights. Currently, there are little judicial regulations as to: How will genetic tests be evaluated and regulated for accuracy, reliability, and utility? How do we prepare healthcare professionals for the new genetics? How do we prepare the public to make informed choices? How do we as a society balance current scientific limitations and social risk with long-term benefits? Many decisions have been taken by the courts on the gene therapy and observations made in this context (see Mehlman 1999). There are many common problems and decisions related to genetic mapping for clients served by therapists and lawyers. After reviewing crucial legal issues and doctrines that apply to family life and therapy that have already arisen, Aldrich (2002) is of the opinion that current legal doctrines will need to be rearranged, and therapists will have to deal with the emotional result of the medical and legal decisions.

There is another major issue, "Who should have access to personal genetic information, and how would it be used and affect an individual and society's perceptions of that individual?" It also requires proper judicious handling. Subjects have the right of privacy and confidentiality of genetic information. There is a fear of psychological impact and stigmatization due to an individual's genetic characterization. The U.S. Department of Energy (DOE) and the National Institutes of Health (NIH) devoted 3% to 5% of their annual HGP budgets toward studying

the ethical, legal, and social issues (ELSI) surrounding availability of genetic information and have highlighted many of these issues. A number of conferences have been held on the above issues.

Anthropologists can look into provide various types of input on these issues and also on the conceptual and philosophical implications regarding human responsibility, free will vs. genetic determinism, and concepts of health and disease. They can inquire into questions like: Do people's genes make them behave in a particular way? Can people always control their behavior? What is considered acceptable diversity? Where is the line between medical treatment and enhancement? There are issues of minority rights and impacts of HGP on minority communities (see Zilinskas and Balint 2001).There has to be adequate safeguards for using genomic information in health and disease.

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