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Genetic Markers in Human Blood

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ABSTRACT The human population genetics incorporates study of biology and environmental factors, as well as the forces of micro-evolution leading to macro-evolution, which ultimately influences the structure of human populations. In the present paper and attempt has been made to a give a brief review of the genetics and distribution of some of the polymorphic traits - blood groups, human leucocyte antigens, serum proteins, red cell enzymes, haemoglobins and DNA.

INTRODUCTION

Biological Anthropology deals with the comparative biogenetics of man. Within the various fields of research of the present Biological Anthropology the study of human evolution as well as the study of genetic variation in modern man hold an eminent place. An important branch of Biological Anthropology is therefore Population Genetics, which deals on the one hand with exact genetic descriptions of human population, but which on the other hand tries to find out the reasons for genetic differences among them. To study these genetic differentiation processes in man, which are obviously still ongoing, reliable population data are necessary. As far as the various genetic markers of the human blood are concerned such comprehensive reviews have been given *e.g.* by Mourant et al. (1976), Steinberg and Cook (1981), Tills et al. (1983), Roychoudhury and Nei (1988) and Walter (1998). The existence of genetic variation in man is caused by many factors, among which selection, migration and gene flow, genetic drift and founder effects are the most important ones. By means of many examples, Vogel and Motulsky (1997) have shown the importance of these factors for the understanding of genetic variation in man. Mourant et al. (1978) have reviewed the associations between genetic markers of the blood and diseases, which are of considerable interest in this connection.

Recently there is an explosion of studies using several DNA markers to study the genetic variability and phylogenetic relationships of human populations (Cann 2001; Basu et al. 2003; Cavalli-Sforza and Feldmann 2003; Kivisild et al. 2003; Cordaux et al. 2004; Jorde and Wooding 2004; Reddy 2008). Now many phylogenetic trees on world wide human populations are put forth using the mtDNA and Y chromosomal DNA markers to understand the evolution of modern human (Wallace 1995; Hammer et al. 1997, 1998; Hammer and Zegura 2002; Underhill et al. 2000, 2001; Underhill 2003; Bamshad et al. 2004; Cavalli-Sforza 2005; Hunley and Long 2005; Rower et al. 2009; Alakoc et al. 2010; Grskovic et al. 2010; Serin et al. 2011 among others.)

The use of polymorphic DNA segments as markers for diseases has greatly expanded the potential utility and has already contributed considerably to our knowledge of human genome pathology (Reich et al. 2001; Collins et al. 2003; Wall and Pritchard 2003; McVean et al. 2004; Tishkoff and Kidd 2004; Takeshima et al. 2010; Anesi et al. 2012; Yang et al. 2013; Maller et al. 2013; Yang et al. 2013 among others).

The unit of study is genetic variation in man is a "breeding population", also referred to as a "Mendelian population". Following Harrison (1988) one can point out that "the collective unit of evolution is the population and it is in populations that all the forces we have considered operate" (p. 326). Thus selection, gene flow, genetic drift, founder effects etc. are acting on and in populations and shape their specific genetic profiles in the course of time. The "breeding population" is the minimal integrated unit of evolutionary changes. As far as delineating evolutionary factors are concerned, the "breeding populations" as a unit of study meet almost every logical requirement unit and any change in its genetic profile from one generation to the next will constitute an evolutionary change.

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The impact of the population approach on the study of genetic variation in man has been to focus attention on "breeding populations" as biological or evolutionary units in man and to describe them in terms of gene frequencies or if this is not possible (anthropometric, morphological, dermatoglyphic, etc. traits) in terms of phenotype frequencies and mean values, respectively. Such exact and comprehensive descriptions are the basic requirements for the understanding of genetic variation in man and thus for the analysis of the various evolutionary factors, which caused this variation in the course of time.

The populations of India and other South Asian countries offer great opportunities to study genetic variability. Perhaps, nowhere in the world people in a small geographic area are distributed as such a large number of ethnic, caste, religious and linguistic groups as in India and other South Asian countries. All these groups are not entirely independent, people belong concurrently to two or more of these groups. People of different groups living side by side for hundreds or even thousands of year try to retain their separate entities by practising endogamy.

The aim of the study is to have a satisfactory knowledge of micro-evolutionary processes as they are reflected in genetic traits in human populations.

For the present study genetic markers in human blood are classified into the following groups:

1. Blood Group Polymorphisms
2. Serum Protein Polymorphisms
3. Red Cell Enzyme Polymorphisms
4. Haemoglobin

For more details readers are referred to the works of the various authors (Giblett 1969; Yunis 1969; Vogel and Helmbold 1972; Race and Sanger 1975; Harris and Hopkinson 1976; Mourant et al. 1976a, 1978; Harris 1980; Steinberg and Cook 1981; Tills et al. 1983; Mourant 1983; Livingstone 1985; Yoshida and Beutler 1986; Roychoudhury and Nei 1988; Walter 1998), for blood group terminology (Lewis et al. 1990) and for guidelines for human gene nomenclature (Shows et al. 1987).

Identify and Distinguish the People

For the biogenetical study of the population, researchers have generally used the following criteria to identify and distinguish the people:

1. Regional Groups,
2. Ethnic Groups,
3. Linguistic Groups, and
4. Religious Groups.

It should, however, be kept in mind that these are the convenient units of study, although there are significant levels of overlapping between them. For example, an occupational group pursuing traditional job inhabits a region, shares religion with other categories, belongs to one or the other language group and has an aggregation of ethnic properties. But in the human population genetic studies, out of these criteria one is chosen (Bhasin 1988).

1. Regional Groups: These can be divided into the following groups:

a. Natural Regions: The natural regions have broad uniformity in their characteristics, such as relief, geomorphological history, drainage, climate, soil, natural vegetation and wild life.

b. Climatological Factors and Climatic Regions: Various climatological factors (Rainfall, Humidity, Temperature) and Altitude have been considered to study correlations with different biological traits. A climatic region generally possesses a broad uniformity in climatic conditions produced by combined effects of climatic factors

c. Political Divisions: A country is comprising of number of states, districts etc. For example, India iscomprising of 29 States and 6 Union Territories. In free India the distribution pattern of major language groups was considered as a satisfactory basis for the formation of states. This has given a new political meaning to the geographical patterns of the linguistic distribution of the country.

2.. Ethnic Groups: An aggregation of biological and socio-cultural characteristics constitutes an ethnic group. For example in India within the category of Ethnic Group, one may include Castes, Scheduled Castes, Scheduled Tribes and Communities. Community generally refer to a group of people who may have occupational, linguistic, religious or regional characteristics (Bhasin 1988).

3. Traditional Occupational Groups: In the traditional society, there were occupational guilds. For example in India, the *Chaturvarna* system with its division into *Brahman* (priestly caste), *Kshatriya* (warrior caste), *Vaishya* (land owners and traders) and *Sudra* (labouring caste) was based on occupational differentiation. The occupations are graded - manual labour is looked down upon, and those dealing with swine-herding, scavenging, butchery, removal of night soil are regarded as polluting (Bhasin 1988). The

caste based division of occupation is 1. Priesthood, 2. Warfare, 3. Trade and Commerce, 4. Agriculture, 5. Animal Husbandry, 6. Artisan, and 7. Menial Workers.

4. Linguistic Groups: Linguistic diversity is an important factor in the formation of regional groups, and it also reflects the regional differentiation. There are quite good number of languages and innumerable dialects which change after few scores of kilometers. A linguistic group is an entity of social significance. There is a broad social integration among all the speakers of a certain language. In the beginning languages and dialects developed in the different regions of the country under conditions of more or less isolation. The language and the dialect thus play a significant role in defining the elements of regional identity.

1. BLOOD GROUP POLYMORPHISMS

1.1. The ABO-System

Landsteiner (1900, 1901) recognised the existence of the ABO blood group system, in humans comprising A, B and O groups. Decastello and Sturli (1902) discovered the fourth group AB, of the system. In later studies it was possible to subdivide A group into A1 and A2 (v. Dungern and Hirszfeld 1911) and A3 (Friedenreich 1936). The mode of inheritance of ABO groups (Bernstein 1924) and further A1, A2 subgroups (Thomsen et al. 1930; Friedenreich and Zacho 1931) has been well established. Existence of differences in the allele frequencies of the ABO blood groups from one population to another was first noted by Hirszfeld and Hirszfeld (1919) and this was followed by many extensive studies on various populations of the world for this system. The ABO locus is assigned to the distal end of the long arm of human chromosome 9 (9q34.1-q34.2). It is linked to the loci for nail-patella syndrome (Renwick and Lawler 1955) and adenylate kinase (AK) (Rapley et al. 1967).

The rare 'Bombay' or Oh phenotype described by Bhende et al. (1952) is peculiar both in red cells and in serum: the cells are not agglutinated by anti-A, anti-B or anti-H and serum contains anti-A, anti-B and anti-H. The cells are usually LE(A+). The 'Bombay' phenotype is not known to have any disease associations except for the fact that persons of this type have a strong anti-H antibody which causes difficulties if they need blood transfusion. From India, 62.6 per cent of the 179 cases reported for typical Bombay phenotype are from Maharashtra, out of which 40 per cent cases are from Maratha Community alone. From Southern part of India 14 cases have their origin in Karnataka and 8 in Andhra Pradesh. The number of the phenotype cases reported from South-East Asia especially from India is very large as compared to that reported from Western countries (Sathe et al. 1988).

The association between blood groups A and carcinoma of the stomach was shown by Aird et al. (1953). Since then, extensive research work has been done and more and more blood group systems were examined for associations with diseases. The studies with blood groups other than the ABO system, in general, have shown no associations with diseases except for the Rhesus system associated with haemolytic disease of the newborn. Studies on blood groups and diseases of both infectious and non-infectious types are available and reviewed by Vogel and Helmbold (1972) and Mourant et al. (1978). The studies carried out from the Indian Region on the associations between diseases and biological traits have been recently compiled by Bhasin and Khanna (1991).

The various diseases have been categorized with infectious (bacterial, viral, protozoal), neoplasms, metabolic (diabetes mellitus), mental disorders, circulatory system, blood, digestive system, genito-urinary, skin, eye, congenital anomalies etc. and it has been observed, in general, that persons of group A are much more affected while other groups have an immunological advantage. Only the diseases of digestive system (gastric and duodenal ulcers) are associated with group O but thesediseases are rarely fatal. From India, it has been observed that group B persons seem to be at a greater risk of disease as compared to group A (Murty and Padma 1984). However to study the association between diseases and polymorphic systems among the populations of the Indian Region care should be taken on the question of choice of the disease and control groups due to ethnic diversity and variation in the incidence of diseases and allele/haplotype frequencies of the genetic traits in the compared groups.

The adaptive functions of blood groups have been studied with regard to professions wherein Jörgensen (1972) observed that seniles of 75 years of age and above, active soldiers, active athletes of 40 years and above, as well as, doctors and

surgeons who are about 65 years or older, all have better fitness within the blood group O.

From the results of the analysis of associations with diseases by probable age of their onset, Padma and Murty (1984) observed that group O is favourable in infancy and childhood and groups A and B in adult life, which shows that there is a process of inversion.

Heterozygotic selection due to ABO incompatibility between mother and foetus is now generally accepted (Mourant 1972; Penrose 1975; Vogel and Motulsky 1997 among others). Chromosomal abnormalities are high in spontaneous abortions (Carr 1971; Bhasin et al. 1973), however, the rate of abnormalities in the earliest abortions, less than eight weeks is surprisingly low (Boue et al. 1984), thus indicating that other mechanisms are also responsible for early abortions. A deficiency of heterozygous incompatible children (Waterhouse and Hogben 1947; Matsunaga 1953) indicates that ABO incompatibility is one of the several factors responsible for pregnancy wastage. If ABO incompatibility is responsible for infertility or subfertility then their representation will be lower than expected among the fertile couples.

The extent to which the variety of polymorphic systems (blood groups, serum proteins and red cell enzymes) in man affect fitness and are thus subject to natural selection, has however remained controversial (Vogel 1970, 1975; Wiener 1970; Reed 1975). Consequently the association of specific disease with polymorphic traits and their impact on differential fertility and susceptibility to change is yet to be determined with any degree of finality.

The most widely studied ABO blood groups show that in general, the allele frequencies of the total population of the world to be *ABO*O* = 0.623; *ABO*A* = 0.215 and *ABO*B* = 0.162 (McArthur and Penrose, 1950-51). The European populations have more than 0.25 of *ABO*A* allele (varies from 0.25 to 0.35) and *ABO*B* allele frequency below 0.10, whereas among the Negroids of Africa allele *ABO*O* is present in high frequency and the frequencies of alleles *ABO*A* and *ABO*B* fall between 0.10 and 0.20. Among the population groups of Southwest Asian countries (Saudi Arabia, Jordan, Kuwait, Yemen, Israel, Lebanon, Syria, Iraq, Iran and Afghanistan) the frequencies of alleles *ABO*A* and *ABO*B* are about 0.23 and 0.15, respectively except in Afghanistan where he allele *ABO*B* is higher than allele *ABO*A*. From East Asia (China, Japan, Mongolia, Korea), the frequency of allele *ABO*A* is generally high (more than 0.20 as compared to allele *ABO*B* (less than 0.20) except among the population groups studied from Mongolia, where allele *ABO*A* (0.15) is less than allele *ABO*B* (0.22). Among Tibetans the frequency of alleles *ABO*A* and *ABO*B* averages about 0.16 and 0.24, respectively. In Southeast Asia (Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, Vietnam), the frequency of allele *ABO*B* exceeds allele *ABO*A* in most of the population groups reported, except from South-East Asian Archipelago (Indonesia, Philippines) where allele *ABO*B* is more (about 0.17) than allele *ABO*A* (about 0.18) in most reported literature. The Australian Aboriginals almost lack the allele *ABO*B*. In Central Asia (Kazakhstan, Kirghizia, Tajikistan, Turkmenia and Uzbekistan) the alleles *ABO*A* and *ABO*B* average about 0.215 and 0.175, respectively (Mourant 1983; Mourant et al. 1976a; Tills et al. 1983; Roychoudhury and Nei 1988; Walter 1998).

*ABO*A2* allele is almost entirely confined to Caucasoid and Negroid populations in whom it is however mostly below 0.05 and only in extreme or rare cases exceeds 0.10. Among the Mongoloids the data on frequencies of *ABO*A2* show it to be rare or absent. In South East Asia the *ABO*A2* allele frequency varies between 0.005 and 0.025. Among Australian Aborigines and the population groups of East Asia the allele *ABO*A2* is absent.

In Southwest Asia *ABO*A2* allele frequency varies mostly between 0.04 and 0.06. In the Indian Region, the *ABO*A2* allele is present nearly in all populations but its average frequency of 0.025 is lower than in Europe (Mourant 1983; Mourant et al. 1976a; Tills et al. 1983).

In India, the distribution of allele *ABO*B* frequency is higher (0.233) as compared to allele *ABO*A* (0.186), whereas the frequency of allele *ABO*O* is 0.581. The value of allele *ABO*A2* is 0.025. Among the ethnic groups *viz.*, castes, scheduled castes, scheduled tribes and communities of India, the value of allele *ABO*B* is high as compared to allele *ABO*A*. However the differences between allele *ABO*A* and allele *ABO*B* frequencies are less among scheduled tribes (*A* = 0.213 and *B* = 0.218) as compared to castes (*A*= 0.179 and *A* = 0.248) and scheduled castes (*A* = 0.181 and *B* = 0.246), whereas the frequency of allele *ABO*O* is almost similar among castes

(0.572), scheduled castes (0.573) and scheduled tribes (0.569). In almost all the studies reported from Eastern Himalayan region, the frequency of allele *ABO*A* is quite high as compared to that of *ABO*B*. In India alleles *ABO*B* and *ABO*A* increase and allele *ABO*O* decreases in frequency from south to north. This is also observed among some scheduled tribes of South India, Central India, West India and a few caste and community ethnic groups from West India. In some of the population groups of Western and Central Himalayas a little high or similar frequency of the *ABO*A* allele is observed to that of *ABO*B*. The frequency of allele *ABO*A2* is 0.025 among different population groups of India. In the various language families the pattern of distribution is almost similar *i.e.*, high frequency of allele *ABO*A* in Tibeto-Chinese language family followed by Austro-Asiatic and low in Dravidian language family. Whereas in Indo-European speakers, there is little variation in frequency of allele *ABO*A*, but a steady rise in allele *ABO*B* and a fall in allele *ABO*O* is observed. ABO gene distribution is without doubt influenced by selection *via* smallpox, cholera and plague. It has been suggested that the advantage of group B could be due to long-standing selection against type A by smallpox as well as against type O by both plague and cholera (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

1.2. The MNSs-System

The works of Landsteiner and Levine (1927a, 1928), Schiff (1930), Wiener and Vaisberg (1931), Sanger and Race (1947), Sanger et al. (1948) and Levine et al. (1951) have significantly contributed to our present understanding of the MNSs blood group system. The antigens M, N, S and s of this system have been shown to be inherited characters. The system has been studied extensively now in many parts of the world; the earlier reports usually making use of anti-M and anti-N and recent ones also of anti-S, with or without anti-s. Subdivision of M and other variants of M and N antigens have been reported (for detail *see* Race and Sanger 1975). The MNSs locus has been suggested to be situated on the long arm of chromosome 4 (4q28-q31). MN groups are of very little clinical significance (Mourant et al., 1978).

Among most of the populations studied the frequency of allele *MN*M* varies less *i.e.*, from 0.50 to 0.60. The populations of Europe and Africa are not greatly different from each other in the distribution of alleles *MN*M* and *MN*N*, as allele *MN*M* varies from 0.50 to 0.60 among Europeans and in Negroids the alleles *MN*M* and *MN*N* frequencies are roughly equal to one another. In Southwest Asia, the frequencies of allele *MN*M* are high almost everywhere and a quite high frequency is observed from Saudi Arabia (very high frequencies are reported among American Indians and Eskimos). From Southeast Asia also high frequencies for allele *MN*M* are reported. In Thailand and Myanmar allele *MN*M* averages about 0.65 and in Laos, Cambodia and Malaysia it isabout 0.76, 0.78 and 0.72, respectively, however allele *MN*M* frequencies are observed to be low in Vietnam (0.58), Philippines (0.050-0.60). From East Asia the allele *MN*M* frequencies average about 0.55 in most of the population groups, whereas among Tibetans, the frequency of allele *MN*M* is above 0.63. From Central Asia, the allele *MN*M* frequency averages about 0.60. Among Australian Aborigines, the frequency of allele *MN*N* is higher than *MN*M* (Mourant 1983; Mourant et al. 1976a; Tills et al. 1983; Roychoudhury and Nei 1988; Walter 1998). The frequency of the allele *MN*M* is high in the Indian Region and this is one of the main ways in which its peoples differ serologically from the Mediterranean people (Mourant et al. 1976a).

Among Indian populations, the frequency of allele *MN*M* is 0.648 (range 0.445 to 0.898), which is similar to that present among Asian populations, in general. In various ethnic groups of India, the frequency of allele *MN*M* is quite high among scheduled tribes (0.692, range from 0.448 to 0.898) as compared to other groups among whom it is less than 0.65 (Bhasin 2009; Bhasin et al. 1994).

Antigen S, the product of one of a pair of allelic genes **S* and **s* is very closely linked to both *MN*M* and *MN*N*, but is found more in association with *MN*M* than with *MN*N*. In European populations about half the *MN*M* alleles is associated with *S* and the other half with **S*, while of the **N* alleles about one sixth are associated with *S* and the rest with *S* (Mourant et al., 1976a). In Africa, the **s* allele, however, is considerably rarer than in Europe and is rather more evenly distributed in its linkage between M and N than in Europe. The frequency of haplotype *MNS*MS* is about 0.23 among Europeans. In Southwest Asia, allele *MN*M* is higher than in Europe and is usually associated with **S* (the *MNS*MS* and *MNS*NS* are 0.26 and 0.08,

respectively). After American Indians the highest frequency of *MNS*MS* is observed from Saudi Arabia. From the Indian Region the frequency of *MNS*MS* is little less than 0.20.

The frequency of **S* is low in Far East, as among the population groups from Korea haplotype *MNS*MS* is about 0.05 and *MNS*NS* - 0.01, whereas in Japan **S* is more associated with *N* than *M* (*MNS*MS* - 0.025 and *MNS*NS* - 0.167), and also in Southeast Asia where *MNS*MS* and **NS* are 0.03 each. However, among the Tibetans the frequency of *MNS*MS* is high 0.14 as compared to Southeast Asian populations. In Central Asia *S* is more associated with **N* rather than **M* as the average frequencies of haplotype *MNS*MS* and *MNS*NS* are 0.31 and 0.32, respectively. **S* is completely absent in Australian Aborigines (Mourant et al. 1976a; Tills et al. 1983).

Among Indian populations the frequency of allele **S* is little less than 0.30 and is present mainly in the haplotypic combination of *MNS*MS*. The haplotype frequencies of *MNS*MS* and *MNS*MS* are quite high (0.195 and 0.452, respectively) as compared to *MNS*NS* and *MNS*MS* (0.092 and 0.247, respectively). In fact, in all the different ethnic groups of India, the haplotype *MNS*MS* is greatly in excess of *MNS*NS* as has been observed among other Caucasoid populations.

A low frequency of haplotypes *MS* and NS has been observed among population groups from Eastern Himalayan region (0.099 and 0.045, respectively). In the various language families the distribution of these haplotypes shows similar pattern as observed among populations from various zones of India, regions of Himalaya and ethnic groups. Austro-Asiatic speakers are showing closer proximity with Dravidian speakers, whereas Tibeto-Chinese speakers of Mongoloid affinities and Indo-European speakers of Caucasoid origin show considerable variations in the frequencies of the MNSs haplotypes (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

1.3. The P-System

Landsteiner and Levine (1927b) discovered the P blood groups by immunization experiments. The P antigen was shown to be inherited in all probability as a Mendelian dominant character (Landsteiner and Levine, 1930, 1931). Levine et al. (1951) and Sanger (1955) reported antigen Tja as part of the P system. This discovery altered all original notation: the phenotyhpe P+ became P1; the phenotype P-became P2 and anti-P became anti-P1. The rare phenotype P, originally called Tj(-) was described by Levine et al. (1951). The P locus has been assigned to the autosomal chromosome 22q11.2-qter.

Alleles at the P locus are involved with fertility differences or spontaneous abortion. Women of genotype pp, who always have anti-P+ and anti-P1 in their plasma, are particularly subject to abortion, apparently resulting from the action of the antibody upon the almost invariably P positive foetus (Mourant et al. 1978).

The frequency of allele *P*P;* is highest (0.80) among Negroes, whereas among population groups of Europe, Southwest Asia and Southeast Asia the frequencies are almost similar, about 0.50, 0.45 to 0.55 and 0.50 to 0.55, respectively. However quite low frequencies of the allele (range 0.15 to 0.23) have been reported from East Asia and similar frequency has been reported among American Indians. In the Indian Region, the frequency of allele *P*P* is almost similar to that observed among Europeans (Mourant et al. 1976a; Tills et al. 1983; Walter 1998).

Among Indian populations, allele frequency is 0.416 (varies from 0.045 in West Bengal to 0.704 in Maharashtra) and is almost similar to that observed among populations from Europe, Southwest Asia and South-east Asia. The frequency of allele *P*P* is quite low in the Himalayan mountain complex populations (0.238) and this may be due to Mongoloid admixture present among them and also since similar frequency is found in East Asian populations, whereas, in rest of the regions the frequencies fall in the same range as observed from Europe, Southwest Asia and South-East Asia. In the ethnic groups, low frequency of this allele is observed among scheduled tribes (0.375) and high frequency in communities (0.474). In the different language families the highest frequency of *P*P* is observed in Dravidian language family (0.489) and lowest in Tibeto-Chinese language family (0.175). It shows that the frequency of allele *P*P* is high in South India and starts decreasing towards north and north-east India and gets quite low in the Himalayan region (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter, 2001).

1.4. The Rhesus-System

The discovery of Rhesus (Rh) blood groups (Landsteiner and Wiener, 1940) and its role in

erythroblastosis foetalis (Wiener and Peters 1941; Levine et al. 1941) was one of the greatest advancements in the history of human serology. Fisher's synthesis of Rh gene complex, the CDE system (Fisher 1944) and Wiener's (1943) and others classification in terms of Rh-Hr and R with indices and suffices are quite different and are found to be insufficient to incorporate the surfeit of more recent findings of complex antibodies and antigens in the system. A numerical Rh notation system free from any genetical implications was developed by Rosenfield et al. (1962, 1973). A number of Rh variants have been reported. The first human blood found to lack all known antigens, Rh null was found by Vos et al. (1961). The Rh groups are known to be involved in the process of natural selection due to mother-foetus incompatibility leading to haemolytic disease of newborn, or foetal loss. The diseases that show association with Rhesus system are typhoid and paratyphoid infections which show highly significant deficiencies of Rh-positives (*i.e.*, excess of Rh-negatives), pulmonary tuberculosis, other forms of tuberculosis and sacoidosis also show a deficiency of Rh-positives, which for infections of bone and joints and those of the genito-urinary system is statistically significant (Mourant et al. 1978). Virus diseases show in general a deficiency of Rh-positives, which is significant for mumps, infectious mononucleosis and viral meningitis (Pacirorkiewiscz 1970). Duodenal ulceration is one of the few diseases which shows a significant association with Rh groups. The combined relative incidence D+/D- is 1.11 (Mourant et al. 1978). The Rh loci have been assigned to the short arm of autosomal chromosome 1 (1p36.2-p34). The complex genetics of the Rhesus system with a high degree of polymorphism greatly stimulated their studies in world populations.

In Europe, there is a steady decline in *RH*D* frequency from about 0.70 in the east to 0.55 in the west and to 0.50 or less in Basques. Among the population groups from Africa, the frequency of *RH*D* allele varies around 0.80 though it is much higher in a few populations. In Southwest Asia, the frequencies of *RH*D* allele are in between 0.68 and 0.75 in most of the population groups. In Southeast Asian populations it is highest except in South Asian Archipelago where allele *RH*D* is around 0.90. From East Asian region the allele *RH*D* averages more than 0.90. In most of the peoples of central Asia *RH*D* allele is rare or absent however from Tajikistan and Uzbekistan the allele has been reported more than 0.20. The allele *RH*D* is absent among Australian Aborigines (Mourant et al. 1976a; Tills et al. 1983; Roychoudhury and Nei 1988; Walter 1998).

Among Indian populations the frequency of allele *RH*D* averages around 0.803 (varies from 0.532 to 1.000). It is highest among the scheduled tribes (0.86) as compared to other ethnic groups. The frequency of allele *RH*D* is high in the Himalayan mountain complex (0.813) and it is highest in the Islands region (0.996). The pattern is similar as observed in Southwest Asian, East Asian and Southeast Asian populations (Bhasin 2009; Bhasin et al. 1994).

The antigen D is located on the erythrocyte surface, as are other numerous RH specificities. Antigens C, c, E and e are the best known, but more than 15 have been defined, which render the Rhesus system very complex. Two hypothesis have been proposed for its system of inheritance. According to Fisher (1944), the Rhesus system includes three loci *D, C* and *E* having alleles *D* and *d* (the latter being recessive), *C* and *c* (codominant), *E* and *e* (codominant), respectively. Wiener (1943) on the contrary, considered one single locus having pleiotropic effects. These two hypothesis gave the two different nomenclatures. Both models can be considered as equivalents since they do not influence the interpretation of phenotypic observations. Fisher's three loci are closely linked, and the resulting haplotypes follow a one-locus Mendelian transmission. Only one crossing-over event has been observed, though with some reservations (Steinberg 1965). These rare recombination events, however, may be responsible for different haplotype origins in the human species, as suggested by Fisher (1947a, b, 1953) and Fisher and Race (1946). The three most common European haplotypes *CDe(R1), cDE(R2),* and *cde (r),* could have given the less frequent *Cde(r'), cdE(r"), cDe*(R^o) and *CDE (RZ).* The *CdE*(*ry*) haplotype would have required two recombination events from the original ones to appear. This would explain its extreme rarity in actual populations. A complementary inheritance model involving an open regulative structure has since been proposed (Rosenfield et al. 1973). In the present study only well known haplotypes *RH*CDe, RH*cDE, RH*cDe, RH*CDE, RH*cde, RH*Cde, RH*cdE* and *RH*CdE* have been considered.

In Europe most of the northern and central European populations differ slightly, where the

frequencies of haplotypes *RH*CDe(R1), RH*cde(r), RH*cDE(R2)* and *RH*cDe* (*R0*) are around 0.40, 0.40, 0.15 and 0.03, respectively and *RH*Cde(r'), RH*cdE(r")* frequencies are both about 0.01 and *RH*CDE* (RZ) is almost absent, whereas in Southern Europe and Mediterranean area *RH*cde* and *RH*cDE* are usually lower (about 0.20 and 0.08, respectively) and *RH*CDe* is higher (about 0.60) than northern and central Europe. In Africa, the Negroes have about 0.60 of *RH*cDe* and 0.20 of *RH*cde*. Among the population groups from Southwest Asian and Indian Region the distribution of Rhesus frequencies is almost similar to that observed from the Mediterranean region, but with a marked admixture of African genes in the Arab countries. In East Asian population groups, *RH*cde* is rare or absent and *RH*CDe* and *RH*cDE* are predominate (about 0.70 and 0.20, respectively) and *RH*cDe* and *RH*CDE* are often present. In Southeast Asia, *RH*CDe* is quite high (more than 0.70) and *RH*cDE* (about 0.10) and *RH*cDe* (about 0.05) are also present. Among Tibetans *RH*cDE* is present in quite high frequency (0.32) and *RH*CDe* is present at about 0.56. The *RH*CDE* is commoner (about 0.10) in Australian Aborigines than in any other major group of populations except the American Indians, and the frequency of *RH*CDe* is 0.50, and *RH*cDE* and *RH*cDe* vary considerably among them (Mourant 1983; Mourant et al. 1976a; Roychoudhury and Nei 1988; Walter 1998).

Among the various Indian population groups the highest frequencies are observed for *RH*CDe* (range 0.340 to 0.960, frequency 0.632) and *RH*cde* (range 0.000 to 0.444, frequency 0.177). Against that, all the other Rh haplotypes are showing much lower frequencies as is seen from the following figures:

*RH*cDE*	0.097	(0.000-0.366)
*RH*cDe*	0.056	(0.000-0.413)
*RH*CDE*	0.012	(0.000-0.133)
*RH*Cde*	0.021	(0.000-0.173)
*RH*CdE*	0.001	(0.000-0.036)
*RH*cdE*	0.004	(0.000-0.091)

Among the scheduled tribes, a considerable high frequency of *RH*CDe* (0.707) and low frequency of *RH*cde* (0.093) have been observed. From the various zones the haplotype *RH*CDe* is high in Islands followed by East India as compared to Central, South, West and North India. On the other hand, *RH*cde* is absent in Islands but high frequency of this haplotype is observed from West followed by North, South, Central and East India. In the Himalayan region, the frequency of *RH*CDe* is high and that of *RH*cde* low particularly in the Eastern Himalayan region. Quite interesting results have been observed among populations with Mongoloid affinities for haplotype *RH*cDe*- African haplotype which is present in high frequencies, not yet been observed, in general, in other parts of the world. In the various language families, frequency of *RH*cde* is low and that of *RH*CDe* high among speakers of Austro-Asiatic and Tibeto-Chinese language families as compared to Dravidian and Indo-European language families, and *RH*cDe* is high among speakers of Mon Khmer group and *RH*cDE* in Tibeto-Chinese languages(Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

1.5. The Lutheran-System

The Lutheran blood groups were reported by Callender et al. (1945), Callender and Race (1946), Cutbush and Chanarin (1956). The notation proposed was: allele *LU*A* and *LU*B*, antibodies anti-LUA, anti-LUB. Crawford et al.(1961) and Darnborough et al.(1963) reported dominant LU (A-B-) and recessive LU (A-B-), respectively. Tippett (1963) recognised the relationship of the Lutheran groups with the Auberger groups. In 1951(b), Jan Mohr reported linkage between the Lutheran locus and that for the secretor status and in 1954 reported two further linkages of myotonic dystrophy with Lutheran and Secretor status. The location of Lutheran locus has been suggested on the chromosome 19q12-q13.

The frequency of *LU*A* allele is about 0.04 in Northern Europe, whereas in Mediterranean area the frequency falls to about 0.02. In Africa though the frequencies are variable the *LU*A* allele is about 0.04. Among most of the populations studied from East Asia and Southeast Asia, the allele *LU*A* is absent or is rare and in Southwest Asia its frequency is very low (Mourant et al. 1976a; Roychoudhury and Nei 1988; Walter 1998).

The allele *LU*A* is absent among most of the population groups reported from India, and among those in which it has been observed, the frequency is low *i.e.*, in general its frequency is 0.016 in population groups of India, albeit high frequency (0.033) is found among scheduled tribe groups. The frequency is highest among speakers of Tibeto-Chinese followed by Indo-European

languages; among Dravidian speakers the allele is almost absent. More studies are required to evaluate the precise distribution of Lutheran system in Indian populations (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

1.6. The Kell System

The Kell blood groups which appeared simple initially (Coombs et al. 1946; Wiener and Sonn-Gordon 1947; Levine et al. 1949) have gradually been shown to have a complexity comparable to that of MNSs and Rhesus systems (Race and Sanger 1975). The agglutinins of the Kell system are generally IgG globulins. These agglutinins have been shown to have implications in blood transfusion reactions and in haemolytic disease of the newborn (Jensen 1962; Zettner and Bove 1963; Wake et al. 1969; Donovan et al. 1973). Zelinski et al. (1991) reported that the Kell blood group locus (KEL) is tightly linked to the prolactin-inducible protein locus (PIP) and observed that in view of the regional localization of PIP to 7q32-q36 (Myal et al. 1989), a similar assignment for KEL is favoured (7q32-qter).

Among European populations the *KEL*K* allele is generally found between 0.03 and 0.05, while in Africans this allele is rare. The highest known frequency of *KEL*K* allele is reported among Arabs (0.10), but generally it is present around 0.02 among Southwest Asian populations. Among most of the population groups of Mongoloid origin reported from East Asia and Southeast Asia, allele *KEL*K* is almost absent. In the Australian Aborigines also allele *KEL*K* is absent (Mourant, 1983; Mourant et al. 1976a; Roychoudhury and Nei 1988; Walter 1998).

The number of studies available are few as yet for the distribution of Kell system among Indian populations in which the *KEL*K* allele is either absent or present in low frequency, except different caste groups and Moslem communities from West Bengal among whom the frequencies are reported surprisingly quite high (0.144 to 0.244) (Chakraborty et al., 1975). The average frequency among Indian populations is 0.038 which is similar to that observed among Europeans. The frequency is quite low among scheduled tribes (0.024) as compared to other ethnic groups (varies from 0.040 to 0.044). Among the populations with Mongoloid affinities from the Himalayan region the frequency of allele *KEL*K* is low (0.014). The speakers of Dravidian and Tibeto-Chinese languages with low frequencies (0.010 and 0.017, respectively) show marked differences with Indo-European language speakers with high frequency (0.041). However, in view of only few studies available it is not yet possible to fully evaluate the variation of this genetic marker in India (Bhasin 2009; Bhasin, et al. 1994; Bhasin and Walter 2001).

1.7. The Duffy System

The Duffy antigens *FY*(A)* and *FY(B)* were discovered by Cutbush et al. (1950) and Ikin et al. (1951), respectively. A third gene *FY* was reported among Negroes (Sanger et al., 1955). The Duffy system has been expanded by the identification of three variants *FY*3, FY*4* and *FY*5* (Albery et al. 1971; Behzad et al. 1973; Collegdge et al. 1973). Miller et al. (1976) reported that Blacks have FY^- which is frequent among them and is almost absent among Whites and Mongoloids. The former have a complete resistance against the infective agent of territary malaria, *Plasmodium vivax*. It has been observed that the frequency of Duffy negative is absolute among Africans, therefore, how may it be possible that an allele that is usually observed in polymorphic frequencies spread throughout the entire population because of selective advantage. Livingstone (1984) has given an alternative hypothesis. It has been suggested that the pre-existing high frequencies of the Duffy negative allele prevented vivax malaria from becoming endemic in West Africa. It is argued that vivax malaria originated in a primate ancestor and failed to spread through Africa because of the existence of the Duffy negative allele. The Duffy locus has been assigned to the autosomal chromosome 1 (Donahue et al. 1968) and is probably linked with congenital cataract locus (Renwick and Lawler 1963). The exact position of the gene locus is: (1q21-q25).

Among the European populations *FY**A allele frequency is about 0.42. From Southwest Asia, the frequency is around 0.35, whereas among the Mongoloid populations of East Asian and Southeast Asian regions the frequency varies from 0.80 to 1.00. In Central Asia also allele *FY**A is present in high frequency (about 0.90). The lowest frequencies of this allele have been reported in most of the African populations (0.05) which may be explained due to the presence of FY (A-B-) *i.e.*, homozygous for the amorph allele *FY* of the Duffy system in high frequency over -

0.95 of African Negroes are of this type except from South African Republic (Mourant 1983; Mourant et al. 1976a; Roychoudhury and Nei 1988; Walter 1998).

The distribution of the Duffy blood groups shows that allele *FY*A* varies from 0.136 to 1.000 with a general frequency of 0.530 in the various population groups reported from India. The frequency is high among scheduled tribes (0.603) as compared to other ethnic groups. In the Himalayan region particularly in the Eastern Himalayan region, frequency is quite high (0.737). In the language families also similar pattern is observed that is high frequency in Tibeto-Chinese and Dravidian language families. Selective advantage of *FY* allele has been observed against malaria in Africa. Since from India most of the studies reported are using only anti-FY(a), therefore, it becomes rather difficult to evaluate the selection factor in this part of the world. Further, the studies available are indeed very few, and therefore, more data are awaited for a better understanding of the distribution of this system, as well as its selective advantage if any against malaria, under Indian environmental conditions (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

1.8. The Kidd-System

The Kidd blood group system was discovered by Allen et al. (1951) as a result of the investigations of the haemolytic disease of newborn. It was found that antigen JK(A) was independent of the other blood group systems and was inherited by a gene capable of expressing in single or double dose (Race et al. 1951). The antithetical antibody, JK(B) of the system was discovered by Plant et al. (1953). The discovery of phenotype JK (A-B-) by Pinkerton et al. (1959) led to the recognition of a third allele *JK* at the Kidd locus. The Kidd locus is located on autosomal chromosome 18q11-q12.

The frequency of *JK*A* allele is quite high among African populations (around 0.75). From Europe, it is reported about 0.50, whereas populations from Southwest Asian region show a little high frequency *i.e.*, about 0.55 and than those from East Asian region (around 0.45). From Central Asia frequency of allele *JK*A* is above 0.46 (Mourant et al. 1976a; Roychoudhury and Nei 1988; Walter 1998).

The *JK*A* frequency, in general, is 0.529 among population groups of India (varies from 0.309 to 0.817). The frequency is high in North India (0.609) as compared to rest of the zones – East (0.481), South (0.459) and West (0.438) India. Among caste groups the frequency is high (0.628) as compared to other ethnic groups. The *JK*A* allele frequency is high in Western Himalayan region. Among the speakers of Indo-European and Tibeto-Chinese languages from the Himalayan region the *JK*A* frequency is high. However, due to paucity of data it is difficult to interpret the distribution of the Kidd allele frequencies in Indian populations (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

1.9. The Diego-System

The antibody anti-DI A was found in Venezuela where it had been shown to be the cause of haemolytic disease of the newborn (Layrisse et al. 1955). Layrisse et al. (1959) showed the antigen to be independent from most of the established blood group systems. Thompson et al. (1967) identified the antithetical anti-DI B. The antigen DI(A) is practically confined to people of Mongoloid origin (Race and Sanger 1975). The gene locus lies on chromosome 17q12-q21.

The highest frequency of *DI*A* allele is observed among South American Indians (up to 0.40) but is absent among others as well as in Australian Aborigines. Among the populations from East Asian and Southwest Asian regions, the allele *DI*A* is present but not quite so high as observed in South and Central Americas. The highest allele frequencies are found in Koreans and Tibetans (around 0.05). Examples of this blood group have been observed from Southwest Asia and Indian region (Mourant et al. 1976a; Roychoudhury and Nei 1988; Walter 1998).

In India, *DI*A* allele has been usually observed among population groups with Mongoloid affinities. However, a low frequency of this allele has also been observed among the other population groups (scheduled castes and scheduled tribes). In the different language families the frequency is highest among speakers of Tibeto-Chinese languages (0.018), followed by speakers of Indo-European languages (0.015) whereas in Dravidian speakers, the frequency is quite low (0.003). The data available on the Diego system are scanty for drawing any meaningful conclusion of its distribution in Indian region (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

1.10. The ABH-Secretor-System

The ABH antigens present on red cell surface can also exist in a water soluble form in body fluids (Yamakami 1926; Lehrs 1930; Putkonen 1930; Friedenreich and Hartmann 1938; Hartmann 1941) and probably on all endothelial and many epithelial cells (Szulman 1960, 1962, 1966; Holborow et al. 1960; Kent 1964; Sanders and Kent 1970). Extensive studies on the various body secretions have been carried out to understand their ABH secretor status (Race and Sanger 1975). ABH secretion is controlled by alleles *ABH*Se* and *ABH*se*; the allele for secretion (*ABH*Se*) is dominant to that for non-secretion (*ABH*se*). The secretor locus is found on the same chromosome (19 cen-ter) as Lutheran locus (Mohr 1951b, 1954; Sanger and Race 1958; Metaxas et al. 1959; Greenwalt 1961; Cook 1965; Renwick 1968) and these two loci are further linked to that for myotonic dystrophy (Mohr 1954; Renwick et al. 1971; Harper et al. 1972).

Significant associations have been shown to exist between secretor status and certain diseases. Clarke et al. (1956) showed a strong association between non-secretion and both duodenal and gastric ulceration. In rheumatic heart disease and acute rheumatic fever the frequency of non-secretors is raised (Mourant et al. 1978). Wiener et al. (1960) among others have shown that in those cases where the secretor status of infants suffering from ABO haemolytic disease has been ascertained, there is a marked deficiency of ABH non-secretors as compared with the general population.

A selection-relaxation hypothesis has been proposed by Bhalla (1990) to account for the sustained high frequency of non-secretors in the advanced human societies as opposed to the low frequency of recessive allele (*ABH*se*) diminishing to zero in many primitive human societies and its complete absence in apes and monkeys. He suggested a protective role of secreted blood group substances against the deleterious effects of lectins in gastric mucosa.

The frequency of *ABH*Se* allele among the European populations is around 0.51 or slightly higher. The African populations show an incidence between 0.48 and 0.62. In East Asian and Southeast Asian populations the *ABH*Se* allele is about 0.50. From Central Asia, the allele is observed about 0.49. A quite wide range of frequencies for *ABH*Se* allele is observed from the Indian region from where a good number of studies are now available. Among the Australian Aborigines, and also in Eskimos and American Indians, the *ABH*Se* allele frequency is near 1.000 (Mourant et al. 1976a; Roychoudhury and Nei 1988; Walter 1998).

In India, *ABH*Se* allele frequency is 0.524 in general among different population groups of India. From various zones the frequency of *ABH*Se* allele is high from South India (0.589) and Islands (0.579) and low from Central India (0.467). The high frequency of *ABH*Se* allele is observed among castes (0.555) and low among scheduled tribes (0.495). From the Himalayan region, high frequency of this allele is observed in Eastern region (0.589). The speakers of Munda group of Austro-Asiatic family show low frequency (0.477) as compared to the speakers of Dravidian (0.556) and Indo-European (0.514) languages. There are wide differences in the distribution of *ABH*Se* allele in India primarily due to the ethnic diversity of its people derived from autochthonous (Pre-Dravidian), Caucasoid (Dravidian and Aryan) and Mongoloid racial elements (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

1.11. Molecular Characterization of Blood Groups

Biochemical and molecular genetic studies have contributed to our knowledge of blood groups – associated molecules in the past few years. Among the 26 blood group systems presently identified, almost all have a molecular basis and present investigations are oriented towards the analysis of genetic polymorphism, tissue-specific expressions and structure-functions relationships.

The molecular characterization of polymorphism underlying blood group antigens has made enormous advances during the past 15 years (Cartron and Colin 2001). Currently, 26 blood group systems are recognized (Daniel et al. 2001). The antigens of 22 blood group systems are determined by epitopes on proteins. They may function as transport or adhesion proteins, ectoenzymes, or cytokine receptors present on the red blood cell (RBC) surface (Carton and Colin 2001). Recently, the *DOK1* gene determining the Dombrock blood group system (ISBT 014) has also been characterized (Gubin et al. 2000).

Antigens defined by carbohydrate structure, among which ABO, Hh, Lewis and secretor are

the main representative species, are indirect gene products. They are synthesized by Golgi resident glycosyltransferases, which are the direct products of the blood group genes. Many of these enzymes have been cloned and the molecular basis of the silent phenotypes, for instance O, *Bombay, para Bombay,* Le (a-b-) and non-secretor, has been elucidated. However, the glycosyltransferases involved in the biosynthesis of Pk, P and Pi antigens are not yet characterized. A large number of blood group antigens carried by red cell polypeptides expressed at the cell surface are not related to a carbohydrate structure, and these proteins are direct blood group gene products. Most have been cloned and characterized recently, for instance, MN antigens (glycophorin A), Ss antigens (glycophorin B), Gerbich antigens (glycophorin C and D) and antigens encoded by the RH, LW, Kell, Fy, Jk, XG, Lu and XK loci. Other antigens have been located on proteins already identified, for instance Cromer antigens on DAF, Knops antigens on CRI, Indian and AnWj antigens on CD 44, Yt antigens on AchE, Diego, Wr, Rga and Warr on Band 3 and Colton antigens on AQP-1 (water channel). The Scianna and Dombrock systems, which resisted molecular cloning (Cartron 1996) have also been analysed at the molecular level.

1.12. Human Leucocyte Antigen System (HLA)

The term HLA refers to the Human Leucocyte Antigen System, which is controlled by genes on the short arm of chromosome six. The HLA loci are part of the genetic region known as the Major Histocompatibility Complex (MHC). The MHC has genes (including HLA) which are integral to normal function of the immune response. The essential role of the HLA antigens lies in the control of self-recognition and thus defense against microorganisms. The HLA loci, by virtue of their extreme polymorphism ensure that few individuals are identical and thus the population at large is well equipped to deal with attack. Because some HLA antigens are recognized on all of the tissues of the body (rather than just blood cells), the identification of HLA antigens is described as "Tissue Typing" or "HLA Typing" (Shankarkumar et al. 2002a).

The HLA system a highly polymorphic, genetically diverse among human populations has been explored and utilized in various research in applied disciplines such as Medical Anthropology, Genetic Counseling and Forensic criminal investigations all over the world.

Based on the structure of the antigens produced and their function, there are two classes of HLA antigens, termed accordingly, HLA Class I and Class II.. The overall size of the MHC is approximately 3.5 million base pairs. Within this the HLA Class I genes and the HLA Class II genes each spread over approximately one third of this length.

The cell surface glycopeptide antigens of the HLA-A, -B and -C series are called HLA Class I antigens (Roitt et al., 1998).. There are other HLA Class I loci (e.g. HLA-E,F,G,H,J,K and L), but most of these may not be important as loci for "peptide presenters". The cell surface glycopeptide antigens of the HLA-DP, -DQ and -DR loci are termed HLA Class II (Sanfilippo and Amos, 1986)

The polymorphism at the recognized HLA loci is extreme. The frequent HLA antigens in different populations are clearly different. HLA system with different linked loci and more than 140 different determinants is highly polymorphic. It implies that there are enormous number of different possible phenotypes (approximately 200 million) which can be observed in a population. The HLA system polymorphism is due to the multiplicity of alleles encoded by each of the different loci (see Nomenclature for Factors of the HLA System, 2002). Supertypic (broad) antigens could be dissected into subtypes (splits). Population and family studies have shown that thus far, none of the loci have had quite all their possible alleles defined. The inherited unit in the HLA system is a haplotype which is made up of one allele each of the different HLA loci-HLA-A,-B,-C, and DR/DQ/DP. The loci of HLA system are closely associated (linked), as it has been observed that the recombination (crossing over) frequencies between HLA-A and HLA-B and between HLA-B and HLA D/DR are in the range of 0.8-1.0%, whereas that between HLA-B and HLA-C is only 0.2%.

Among different major ethnic groups certain HLA phenotypes appear unexpectedly frequently e.g. A1, A3, B7, B8, Cw7, DR2, DR3 in Europeans. Further certain haplotypes are found much more frequently than would be expected from the known frequency of each allele e.g. A1, B8, Cw7, DR3 or A3, B7, Cw7, DR2 in Europeans. This phenomenon is known as linkage disequilibrium and its degree can be expressed as so called "delta value" that is to say the relationship between

observed and expected haplotype frequencies. Natural selection mechanisms are presumed to be responsible for such linkage disequilibria.

Several workers have reported HLA studies from various populations of World (Imanishi et al. 1992; Clayton and Lonjou 1997) and India (Shankarkumar et al. 1999a,b; Shankarkumar et al. 2000; Shankarkumar et al. 2001; Shankarkumar et al. 2002b,c; Shankarkumar et al. 2003; Mehra et al. 1984; Pitchappan et al. 1984). Further genetic polymorphism in VNTR and STR loci from India (Gaikward and Kashyap 2003; Rajkumar and Kashyap 2003; Agrawal et al. 2003) and World (Pastore et al. 1996; Jin and Zheng 2003) have showed that the same type of genetic heterogeneity exist among individuals from different populations. The HLA system in man has proved a useful marker in certain diseases.

Amiel (1967) reported the associations of an antigen then called '4C' (now recognised as BW35, B18 and B15) with Hodgkin's Lymphoma. This was followed by an almost explosive growth of reports describing significant associations in a number of diseases. HLA system plays a significant role in the success of organ transplantation and platelet transfusion. There are over 40 diseases which are linked to different HLA. haplotypes in man (Stastny et al. 1983).

Thus HLA antigens along with other genetic markers has immense application in human identification for Forensic studies and are of great significance in anthropological and immunological studies.

2. SERUM PROTEIN POLYMORPHISMS

The KM (Inv) and GM Systems

In 1956, Grubb demonstrated by an agglutination inhibition technique that there are inherited differences associated with Gammaglobulin of human serum (Grubb, 1956; Grubb and Laurell, 1956). A few years later, it was shown that the same technique could distinguish a further set of differences controlled by an independent set of alleles (Ropartz et al., 1961), and the agglutination inhibition test as applied to the AM group involves coating of the red cells with AM(+) immunoglobulin with CrCl techniques of Gold and Fudenberg (1967) rather than by using incomplete anti-D for GM and KM systems. These three systems are now known as the GM, KM (Kappa marker, previously referred as Inv(or *Inv*) which stands for 'Inhibitrice Virm') and AM groups, respectively.

Initially the immunoglobulin phenotypes were described by alphabetical notations. However, the growing complexity of these system, clashes of notation and doubts as to synonymy lead to the holding of a WHO sponsored conference. The committee of World Health Organization (WHO 1964, 1976) recommended numerical notation for the antigenic types of these systems.

The Kappa-light chain allotypes KM (1), KM (2) and KM (3) are inherited *via* three alleles *KM*1, KM*1,2* and *KM*1,3*, hence KM (2) does not occur in the absence of KM (1) (Steinberg and Cook, 1981). The KM locus is located on the chromosome 2p12.

The immunoglobulin heavy gamma chain allotypes (GM) are coded by at least three linked genes $\gamma_1\gamma_2\gamma_3$ and γ^3-γ^1-γ^2 (arranged in order on the q 32.3 band of human chromosome 14q32.33) and are separated by at least 60 Kb distance (Kirsch et al. 1982; Migone et al. 1985).

More than 20 different GM allotypes have already been discovered. There are 18 common GM allotypes out of which 4 occur on gamma-1 chains [G1M (1,2,3,17)], one on gamma-2 chains [G2M (23)] and 13 on gamma-3 chains [G3M (5,6,10,11,13,14,15,16,21,24,26,27,28)]. The locations of the allotypes are indicated by the prefixes G1M, G2M, and G3M for gamma-1, gamma-2 and gamma-3 chains, respectively. Genes encoding allotypes at each of the three gamma chain loci are inherited together in units called GM haplotypes. The frequencies of these haplotypes vary dramatically among ethnic groups (Steinberg and Cook 1981); within each ethnic group, only some of all possible haplotypes that could arise by recombination between the three loci actually occur, suggesting that the distribution of haplotypes may reflect the long-term operation of natural selection. Further support for such a view is provided by several studies that have shown associations between GM/KM allotypes and susceptibility to specific antigens (reviewed by Whittingham and Propert 1986).

2.1. The KM System

Antisera to detect KM (2) and KM (3) are in very short supply, therefore virtually all population samples have been tested for KM (1) only.

Among the Europeans, *KM*1* allele frequency is low (about 0.05) as compared to

populations from Africa, East Asia and Southeast Asia among whom the frequency rises up to 0.30. From South west Asia, allele *KM*1* is a little higher as compared to Europeans. The distribution of KM marker among the various populations of the world has been reviewed by Steinberg and Cook (1981) (*see* also Walter 1998).

The general frequency of *KM*1* allele is 0.144 (varies from 0.021 to 0.328) in population groups of India. The high frequency of this allele is observed among scheduled tribes (0.131) as compared to rest of the ethnic groups. High frequency of *KM*1* allele is also observed in theHimalayan mountain complex and low in other regions, suggesting some selective advantage at this complex, but it is difficult to evaluate this marker at this stage due to few studies available. In the different language families, frequency is very high in speakers of Tibeto-Chinese (0.224) as compared to Indo-European (0.099) and Dravidian languages (0.065). As mentioned earlier frequency of *KM*1* is very high among Mongoloid populations and quite low in Europeans, similar pattern of distribution is observed among Indians, *i.e*. quite high frequency among Mongoloids from Himalayan region and the frequency starts decreasing as one moves towards South (Bhasin, Walter and Danker-Hopfe, 1994).

2.2. The Gm System

The most common GM haplotypes around the world and the groups with which they are primarily associated with are as follows:

It is true that ideally one should study the distribution of GM haplotypes with a large number of antigen specificities. There is a common notion that at least five antisera are required to derive maximum information regarding the affinity of populations. However, unless these antisera are raised from the same source against various GM specificities, there could be a number of problems in GM typing. In addition, since some of the populations examined are known to reflect environmental antigenetic load due to their poor socio-economic conditions, use of such extensive battery of GM specificities may show environmental differences, rather than their anthropological affinity (Chakraborty et al., 1987). The worldwide distribution of GM markers has been reviewed by Steinberg and Cook (1981); *see* also Walter (1998).

In most studies only a few reagents have been used on account of the vareity and cost. Therefore the reports are incomplete to give a clear picture of the distribution of these systems. Most surveys reported the genetic polymorphism of GM system only for GM (1), GM (2) and GM (5).

In general, it has been observed that in India the frequency of haplotype *GM*5* is high (0.355) as compared to *GM*1* (0.276), *GM*1,5* (0.269) and *GM*1,2* (0.100). Similar distribution of haplotypes is observed in various zones *i.e.*, North, West and South India except in East India where *GM*1,5* is quite high (0.405) as compared *GM*1* (0.255), *GM*5* (0.219) and *GM*1,2* (0.121).

In general, it has been observed that in India the frequency of haplotype *GM*5* is high (0.355) as compared to *GM*1* (0.276), *GM*1,5* (0.269) and *GM*1,2* (0.100). Similar pattern is observed in various zones of India except in East India where *GM*1,5* is quite high (0.405) and this haplotype is observed in high frequency among scheduled tribe and among the population groups of Eastern Himalayan region. In the different language families also similar pattern is observed *i.e.*, *GM*1,5* and *GM*1,2* in high frequency in Tibeto-Chinese family (0.470 and 0.148, respectively) and in Indo-European and Dravidian language families high frequencies for *GM*5* (0.427 and 0.392, respectively) and *GM*1* (0.281 and 0.282, respectively). In the Munda group of Austro-Asiatic language family high frequency of *GM*1,5* has been observed (0.562) (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

Group	*Common*	*Haplotype*
Europeans	*GM*3,5*	*GM*3;5,10,11,13,14,26,27*
North East Asiatics, Europeans	*GM*1,17;21*	*GM*1,17;21,26,27*
South East Asiatics, American Indians	*GM*1,2,17;21*	*GM*1,2,17;21,26,27*
North East Asiatics	*GM*1,17;15,16*	*GM*1,17;10,11,13,15,16,27*
South East Asiatics	*GM*1,3;5*	*GM*1,3;5,10,11,13,14,26,27*
Back Africans	*GM*1,17;5*	*GM*1,17;5,10,11,13,14,26,27*
Black Africans	*GM*1;5,6*	*GM*1,17;5,6,11,24,26*

1. Gamma-1 and Gamma-3 allotypes [G3M (28) expected] which are separated by a semicolon.

2.3. Haptoglobin (HP) System

Haptoglobin (HP) is a glycoprotein that combines with free haemoglobin from the lysed red cells, thus preventing its excretion by the kidneys. The HP molecule consists of four chains $(\alpha\beta)_2$ linked with disulphide bonds. The HP α-chain is polymorphic with three common phenotypes HP 1, HP 2-1 and HP 2 which can readily be detected by conventional starch gel electrophoresis (Smithies 1955; Smithies and Walker 1955, 1956) and which are controlled by a pair of codominant autosomal alleles *HP*1* and *HP*2*. Further studies have revealed two common electrophoretic Hpα1-subtypes, 1S (slow) and IF (fast), and this enabled Connell et al. (1962) to classify individuals of type 1 into three subphenotypes, HP 1F, Hp 1F-1S and HP 1S, controlled by two sub-alleles *HP*1F* and *HP*1S*. Similarly individuals of haptoglobin type 2-1 could be subtyped into either HP 2-1F or HP 2-1S. Thus, a series of six phenotypes in the haptoglobin system can be recognized. HP α2-chain is assumed to be the result of an unequal crossing over and gene duplication of two HP α1 genes (Smithies et al. 1962). In accordance with this theory, the HP α2-chain has been shown to exist in three different isoelectric forms, 2FS, 2F and 2S with a molecular weight nearly twice that of the HP α1-chain (Smithies et al. 1962; Nance and Smithies, 1963; Connell et al. 1966). The HP β-chain is a glycoprotein exhibiting a high degree of isoelectric heterogeneity. Some rare β-chain variants have been described (Weerts et al. 1966; Javid 1967). Further a number of variants of haptoglobin have been reported in the literature. The HP locus is assigned to the distal part of the long arm of human chromosome 16 (16 q 22.1).

There is some evidence to show that selective forces are operating in haptoglobin system. Occurrence of HP O phenotype (ahaptoglobinaemia or hypohaptoglobinaemia) has been shown in malarial areas (Blumberg, 1963; Trope et al., 1985) and in cases of haemolytic anaemia. A significant association between sickle cell disease and the HP 1 type is reported by Ostrowski et al. (1987). It is therefore likely that HP O in these areas is the result of combination of environmental and genetic factors (Mourant et al. 1976a). The selective mechanism of haptoglobin is also seen in the protection against foetal loss through ABO incompatibility, provided HP 1 compared to HP 2 (Ritter and Hinkelmann 1966; Kirk 1971; Kirk et al. 1970). Several aspects of haptoglobin have been studied in relation to various diseases. Ferrel et al. (1980) studied haptoglobin and altitudinal selection and concluded that "only in haptoglobin in one group study, there is some indication but whether this is a response to altitudinal selection or other factors is uncertain".

The haptoglobin groups are polymorphic in all human populations, two alleles *HP*1* and *HP*2* accounting for three common phenotypes HP 1-1, HP 2-1 and HP 2-2. World values for the *HP*1* allele range from 0.07 to 0.89 (Kirk 1968). Distribution of *HP*1* is highest (0.60 to 0.70) among the population groups of Africa followed by Europeans (0.35 to 0.45) and Asians among whom low frequency is prominent (Kirk 1968; Giblett 1969; Mourant et al. 1976; Tills et al. 1983; Walter 1998). Studies in India show that *HP*1* allele frequency has been uniformly lowest of all populations in the world (Kirk 1968; Giblett 1969; Baxi and Camoens 1969).

Among Africans generally high frequency of *HP*1* is complicated by high incidence of HP O (sera cannot be typed readily and are referred to as hypohaptoglobinaemia) and such persons may be disproportionately of the HP 2-2 phenotype (Kirk 1973). It is well known that HP 2-2 has the least Hb binding capacity (Baxi and Ektare 1969). The incidence of HP O varies only slightly in Indian populations and is rarely greater than 0.05 (varies from nil to 0.131 among Meplahs Muslims reported by Hakim et al. 1972). Thus, the low *HP*1* is a real situation and further corroborates Parker and Bearn's (1961) contention that *HP*1* allele may have arisen in India and the frequency goes increasing towards East (Southeast Asia) and West (Middle East and Europe), as observed by Baxi and Camoens (1969).

A fourth phenotype HP 2-1 (mod), also under genetic control, is usually found in Black African and American Negro populations; elsewhere in the world it is either absent or occurs only with very low frequency. A considerable number of rare alleles have been described *[HP*1CA* (Galatius-Jensen 1958); *HP*J* (Giblett and Brooks 1963; Smithies et al. 1962); *HP*P, HP*L, HP*H* (Robson et al. 1964); *HP*TR, HP*2HAW, HP*AB,* (Giblett 1964); *HP*1D* (Renwick and Marshall 1966) *HP*B* (Giblett 1967): *HP*MB* (Cleve and Deicher 1965; Weerts et al. 1965); *HP*BELL* (Javid 1967)]. One variant HP 2-1 Johnson was reported from Calcutta (Mukherjee and Das 1970).

Seth et al. (1977) reported variants HP 1-P and HP 2-1 (m) as unclassified, presumably wrongly

since these may be identified from the figure in the text. It seems possible that in these cases haemoglobin was not added in the plasma or serum in sufficient quantity, resulting in a confused identification and these might actually be HP 1 and HP 2-1, respectively. By using appropriate techniques two forms of the *HP*1* allele - *HP*1F* and *HP*1S* can be recognised. The *HP*1F* allele is virtually absent in Mongoloid populations but comprises about 0.40 all *HP*1* allele in Europe and approximately 0.60 in Africa (Kirk 1973). From India, the frequency of *HP*1F* is quite low (0.05), reported from Bombay (Mukherjee and Das 1984).

The frequency of *HP*1* is 0.160 in population groups of India (varies from nil to 0.406); the high frequency of this allele is observed in North India (0.208) and low frequency in South India (0.131). The frequencyis low among scheduled tribe groups in general. In the Himalayan region, high frequency of this allele is reported from Western (0.215) followed by Eastern (0.192) and Central (0.160) Himalayan regions. In the language families high frequency is observed in Tibeto-Chinese family (0.189) followed by Indo-European (0.180), Dravidian (0.130) and Austro-Asiatic (0.118) families. In India, hypohaptoglobinaemia (HP O) phenotype has been detected in almost all the population groups studied and high frequency of this is observed from South India - Meplahs Muslims (0.131). It is suggested that this phenotype has some selective advantage in malaria since it is observed in high frequency (0.30 to 0.40) among some population groups from West and Central Africa. However, it is rather difficult to evaluate HP O in relation to malaria in India since it has been found in almost all the population groups from India, albeit in low frequency (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

2.4. Transferrin (TF) System

Transferrin is an iron binding protein present in plasma. Smithies (1955, 1959) showed by starch gel electrophoresis that it exists in the form of genetically determined different variants, migrating at different speeds. A great many genetically determined variants of transferrin are now known, but show no significant differences in their iron binding capacity (Mourant et al. 1976a). The transferrin locus is assigned to the long arm of chromosome 3 (3 q 21). The rarity of the variants in this system suggests that the normal type (TF C) has, under most circumstances, a selective advantage over the rest. On the other hand, in cattle, several alleles of comparable freqency are involved in a complex system of selective fertility (Ashton 1965). Myers and Krebs (1974) have found some differences in the ecological responses of three genotypes—TF C/ TF E, TF E and TF C among rodents. These observations in animals may serve as background for similar work on human populations.

Transferrin in humans exhibit polymorphism and occurs as slow (D) and fast (B) variants besides the common type (C). Transferrin D is widely distributed in Africa; it has also been demonstrated in Australian aborigines in New Guinea, Fiji, Central and South American Indians and Sweden (Mourant et al. 1976a; Tills et al. 1983; Walter 1998). Kirk et al. (1964) stated that the *TF*D* allele may have arisen earlier in the evolution of the transferrin polymorphism and hence its widespread presence in different populations of the world. The fast moving transferrin B type has been reported in the people of Caucasoid origin or Caucasoid admixture.

There are some twenty genetically controlled variants of transferrin, out of which most are rare. In most of the heterozygous types, the TF is accompanied by the common TF C. The various studies reported on TF distribution show that four of the rare types (TF CD1, CDChi, B2C and B0-1C) have a frequency of 0.01 or more. By far the most common TF variants are D1and D Chi. The TF D1 is reported among the aborigines of Australia and New Guinea, Black African populations and American Negroes, while D Chi is reported in nearly all the Mongoloid populations including Amerindians and the heterozygote CD Chi frequencyranges from 0.01 to 0.10 with mean values around 0.05. In Australia TF D1 achieves the highest frequency, with extremely high values in desert areas of South-West. Here 0.30 - 0.40 of persons tested carry *TF*D1* allele either in heterozygote CD1 or homozygote D1D1 combinations (Kirk 1973). Variants of transferrin are rare in India; Kirk et al. (1962a) observed D variants among the Oraons, which were examined critically and found to be indistinguishable from the DChi variant characteristic of Mongoloid populations (Kirk et al. 1964). Among the Raj Gond tribe of Andhra Pradesh a new variant TF DGond was found (Goud 1981).

The introduction of isoelectric focusing (IEF) in the study of blood genetic markers enabled a

more refined and detailed investigation of this system to be carried out than was possible earlier by either starch gel or polyacrylamide gel electrophoresis.

Using isoelectric focussing, a series of TF C subtypes has been disclosed following the initial observations by Kühnl and Spielmann (1978) and Thymann (1978). There are three common sub-alleles (*TF*C1*, *TF*C2*, *TF*C3*) and at least another 13 less common sub-alleles *TF*C4* to *TF*16* (Kornhuber and Kühnl 1986).

Wong and Saha (1983, 1986) reported differences in the total iron binding capacity of TF C1 and TF C2 in man. Cleve et al. (1988) reported that in European and African samples, there was a tendency for slightly higher TF concentrations in the TF C1 subtype than TF C2 subtype, but they added that the correlation was not statistically significant.

An inherited quantitative decrease of TF has been very occasionally found in patients with severe anemia (Heilmeyer et al. 1961; Goya et al. 1972). Healthy individuals presumed to be heterozygous for a TF "null" allele, *TF*D* have also been encountered (Weidinger et al. 1984). Saha et al. (1990b) reported that newborns whose mothers had a history of previous spontaneous abortion had a significantly higher frequency of the C2 variant and the *C2* gene compared with those without any history of spontaneous abortion.

To find out if there is any correlation between variant transferrins and malaria, Pollack (1985) reported that Walter et al. (1983) have analysed the distribution of transferrin C2 and found it to be more frequent in southernly regions of both India and Europe; D transferrins were found to be more frequent in populations near the equator (Walter 1975). Since malaria was endemic in parts of Europe and India and in equatorial areas until a few generations ago, and since the prevalence of malaria correlates with environmental temperature (Wernsdorfer 1980), the possibility that malaria was the cause of the selective pressure for the evolution of transferrin variants deserves scrutiny.

Among Indians, the transferrin allele found in most individuals is *TF*C* while *TF*D* and *TF*B* alleles are present in quite low frequencies (0.008 and 0.001, respectively). The frequency of *TF*C1* subtype of TFC is high among scheduled tribes as compared to populations with Mongoloid affinities among whom a low frequency is observed particularly from the states of Assam and Manipur. The frequency is high in West India and from here it starts decreasing in all directions particularly in East India. The *TF*C3* referred as specific marker of European population is present in high frequency among populations of North India as compared to others. High frequency of *TF*D* is observed in scheduled tribe and scheduled caste populations and it gives high correlations with mean annual temperature. Walter and Bajatzadeh (1971) observed that *TF*D* is more frequent in tropical than in non-tropical regions and in India it is observed high in tropical savannah type climatic region, but this observation may be due to chance since the frequency observed among different population groups is low. In the different language families, frequency of *TF*D* is high in Munda language group (0.025) of Austro-Asiatic language family and Dravidian language family (0.014) (Bhasin 2009; Bhasin, et al. 1994; Bhasin and Walter 2001).

2.5. Group Specific Component (GC) System

Genetic variation in group specific component (GC), an α-2 globulin was discovered by Hirschfeld (1959) using the technique of immunoelectrophoresis. The variants of the protein differ in charge, so that their positions after electro-phoresis can be shown by use of an appropriate antiserum. The phenotypes were referred to as GC 1-1, GC 2-2 and 2-1 and the family study supported the hypothesis that two alleles, *GC*1* and *GC*2* were responsible for these phenotypes (Hirschfeld 1960). Besides these common phenotypes a number of other rare GC variants have been reported - GC X, GC Y (Hirschfeld 1962); GC AB, GC Chip (Cleve et al. 1963); GC Negro, GC Caucasian (Parker et al. 1963); GC Z (Henning and Hoppe 1965); GC Norwegian (Reinskou 1965); GC Bkk (Rucknagel et al. 1968). The existence of GC O, 'silent' allele, has been suggested by Henningsen (1966). The GC locus is assigned to the long arm of chromosome 4 (q12-q13).

Applying the technique of isoelectric focusing in polyacrylamide gels followed by immunodiffusion, Constans and Viau (1977) uncovered further genetically determined complexity of the GC system. The isoelectric focusing patterns revealed six phenotypes (GC 1S, GC 1S1F, GC 1F, GC 2-1S, GC 2-1F and GC 2) due to the existence of two allelic forms of the former allele *GC*1* (*GC*1F* and *GC*1S*) and *GC*2* allele which

showed no heterogeneity, focusing as a single zone. Eighty four rare mutant alleles have been detected with double-bands and single-band variants for the GC system by this technique (Constans et al. 1983).

A correlation of decline in frequency of *GC*2* allele with a degree of insolation of a region was pointed out early by Walter and Steegmueller (1969), Kirk et al. (1963), Daiger and Cavalli-Sforza (1977) and Mourant et al. (1976b). The efficiency of GC2 protein in binding and transporting vitamin D was suggested as a possible factor selecting for high *GC*2* allele frequencies in areas with little sunshine. A number of expectations such as the high *GC*2* frequencies in Asiatics, New Guinea and South American Indians were listed by Mourant et al. (1976b). This trend in *GC** allele distribution, and its exceptions in relation to the degree of insolation are also observed and possibly more clearly in the subgroups in the isoelectric focusing results. The study of binding of vitamin D and its metabolite to the GC subtypes by Constans et al. (1979) has shown differences in the affinity in GC anodal and cathodal bands. Papiha et al. (1986) observed association between high insolation and *GC*1F* frequency with few exceptions.

Kamboh and Ferrell (1986) reported a marked violation in common GC suballele frequencies in different geographic areas which seemed to correlate with skin pigmentation and intensity of sunlight. Pigmented (Black) and keratinized (Yellowish) populations have a relatively high frequency of the *GC*1F* allele as compared to white skin populations. By comparison, non-pigmented and non-keratinized white skin populations are generally characterized by having the maximum values of *GC*1S* allele.

For the distribution of *GC*1F* and *GC*2* Constans et al. (1985) observed that a cline associated with increasing *GC*1F* and decreasing *GC*2* allele frequencies is, without doubt, present between northern and southern regions. However they added, that due to limited knowledge, it is not possible to establish selective pressure.

In nearly all the populations studied so far, *GC*2* allele has a lower frequency than *GC*1* except among Xavante Indians where *GC*2* frequency is 0.56. Among Europeans, the *GC*1* allele frequency is fairly constant averaging around 0.74. African Negroes generally have a high frequency of *GC*1* allele rarely exceeding 0.90, while it is similar to or higher in Asians than those of Europeans.

The distribution of GC suballeles shows an interesting fluctuation in frequencies. The *GC*1S* frequency starts rising from Southeast Asia and East Asia reaching its peak in India, Europe and Middle East, declining again through East Africa and down to South Africa where it has minimum value (below 0.20). In contrast, Africans are characterised as having the highest frequency of the *GC*1F* allele (above 0.60). Values of *GC*1F* fall to below 0.20 in Europeans but rise again in East and Southeast Asia (0.50). Among Chinese and Japanese the frequencies of *GC*1F* are 0.480 (varies from 0.390 to 0.588) and 0.484 (ranges from 0.421 to 0.579), respectively, whereas among Mongoloids of Southeast Asia the frequency is high (0.535, varies from 0.354 to 0.795). However in the Pacific area there are relatively stable values of the *GC*1S* and *GC*1F* each allele having frequencies in the range of 0.27 to 0.40.

Population	*Allele Frequency*		
	*GC*1S*	*GC*1SF*	*GC*2*
Europeans	0.55-0.60	0.10-0.20	0.20-0.30
Africans	0.07-0.17	0.64-0.84	0.06-0.07
Mongoloids	0.15-0.38	0.39-0.80	0.11-0.32
Iraqis	0.59	0.22	0.17
Indians	0.50	0.25	0.25
American Indians	0.29-0.64	0.13-0.47	0.09-0.38
Australian Aborigines	0.59	0.31	0.03
Melanesians	0.25	0.24	0.34
Polynesians	0.30	0.44	0.26
Micronesians	0.21	0.59	0.28

The frequency of allele *GC*1* is observed 0.747 among population groups of India (ranges from 0.591 to 0.911). A wide range of variation is not observed in between the various ethnic groups *i.e.*, 0.733 (caste) to 0.760 (scheduled tribe) and in zones its frequency is high in West India (0.776) and low in North India (0.723). In the Himalayan region the frequency of allele *GC*1* is almost similar in Eastern and Western Himalayan regions (0.756 and 0.752, respectively) than Central Himalaya (0.688). The frequency of *GC*1S* is high from most of the States and Union Territories of India (0.492) as compared to *GC*1F* (0.250). The differences are observed among the populations with Mongoloid affinities for Western Himalayan region among whom *GC*1S* is high as compared to Eastern Himalayan region with low frequency of *GC*1S* and in some populations from this region the frequency of *GC*1F* is higher than *GC*1S*. The Siddi population (African descent) shows

high frequency of *GC*1F* than *GC*1S* as also observed among Africans, whereas in Onges the *GC*1S* frequency is quite high (0.614). In the speakers of different language families the frequency is high in Austro-Asiatic languages (0.768) and low in Indo-European languages (0.737). The frequency of *GC*1* is a little higher as compared to the European populations but quite low as compared to Negroes, and the pattern of distribution is almost similar to that observed among other Asian populations (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

Less Investigated Serum Protein Polymorphisms

In addition to the numerous polymorphic serum protein systems, which have been investigated so carefully in the past decades, there are some more, which have not yet been analyzed as detailed as the conventional ones (e.g. the HP system or the GC system), so that concerning them up to now in general only fewer population studies are available. This applies on the whole also to India. One of the reasons therefore can be seen in the fact, that the typing of these less investigated serum protein polymorphisms is in some cases rather difficult and requires special reagents and equipments.

The serum protein polymorphisms in question are the following: the *ceruloplasmin system* (*CP system*), the *complement system* (*C3 system*), the *orosomucoid system* (*ORM system*), the *properdin factor B system* (*BF system*), the *α2-HS-glycoprotein system* (*AHSG system*), the *plasminogen system* (*PLG system*), the *factor 13 system* (*F13 system*) and *inter-α-trypsin inhibitor system (ITI system).*

2.6. Ceruloplasmin (CP) System

The ceruloplasmin system (CP system) was detected by Shreffler et al. (1967). This protein belongs to the α_2-fraction of the human serum. It is synthezised in the liver and plays obviously an important role concerning the transport and metabolism of the copper. The electrophoretically detectable polymorphism consists of six different phenotypes, which are controlled by three autosomal co-dominant alleles: *CP*A*, *CP*B* and *CP*C*. The gene locus lies on chromosome 3q23-q25. In addition to these three alleles two more are known. One of them - *CP*TH* - seems to be restricted to the Thai population, the other one - *CP*NH* - to Africans. NH stands for New Haven in the United States, where this allele was observed for the first time. From the present studies it is evident, that the *CP*B* allele is the most frequent one in all so far tested populations including India, whereas the *CP*C* allele is everywhere either complety absent or very infrequent. An interesting distribution pattern is seen concerning the *CP*A* allele, as in African populations this allele is obviously more frequent than in all the others. The average frequency of the *CP*A* allele amounts in Europeans to 0.013 (n=1732), in Asians to 0.002 (n=23038), in Amerindians to 0.001 (n=8258), in Inuits to 0.000 (n=578), in Australian Aborigines to 0.002 (n=521), in Papuans to 0.000 (n=1283) and in Oceanians to 0.000 (Melanesians n=183, Micronesians n=370, Maori n=77). In Africans, however, the average frequency of the *CP*A* allele comes to 0.068 (n=5749); the frequencies vary from 0.000 in Egyptians (n=155) and Sudanese (n=200) up to 0.149 in Nigerians (n= 520). Though more population studies are needed to understand the distribution pattern of this allele, one can suppose that the considerable high *CP*A* allele frequencies among Africans are not due to chance. Shokeir and Shreffler (1970) suggested that these high frequencies might be caused byselectively acting factors. They argued that in the heterozygous phenotype CP AB a reduced copper transfer by the CP A ceruloplasmin could restrict considerably the viability of parasites, as e.g. *Plasmodium falciparum*, without disadvantage by a reduced copper transfer in the heterozygous carriers of a *CP*B* allele. According to this hypothesis homozygous carriers of the *CP*A* allele would be disadvantaged by a strong transfer reduction and would have a reduced fitness. An advantage of heterozygotes could be responsible for the relatively high frequency of the *CP*A* allele in Africa, especially in those regions, in which diseases such as malaria are widespread. However, until now a verification of this hypothesis considering malaria morbidity and mortality among the carriers of the various CP phenotypes is still standing out. It would be of considerable interest therefore to type this polymorphic serum protein system in further tropical populations and to check this assumption.

The Indian data have been compiled by Roychoudhury and Nei (1988) and Bhasin, Walter and Danker-Hopfe (1992); some new data were published recently by Ramesh and Verraju (2000).

The regional variability of CP allele frequencies is observed in India. It is to be seen from these figures that the *CP*B* allele is everywhere by far the most frequent one. Rare CP alleles were found in some populations from West and East India, e.g. in Parsis (*CP*A*=0.019, n=363) and Iranis (*CP*A*=0.030, n=33) from Bombay and a tribal populations (*CP*A*=0.013, n=155) from Bankura, Purulia, West Bengal. For further details see Bhasin et al. (1992). The hitherto published data do not point to any specific regional or ethnic distribution pattern concerning the incidence of rare CP alleles in India (Bhasin and Walter 2001).

2.7. Complement (C3) System

Among the complement systems it is the C3 system, detected by Wieme and Demeulenaere (1967), which plays insofar a particular role as in contrast to the other complement systems it shows clear variations in the ethnic distribution of allele frequencies. Using electrophoretic methods three standard phenotypes can be demonstrated: C3 F, C3 FS and C3 S. They are controlled by two autosomal co-dominant alleles: *C3*F* and *C3*S*. The gene locus lies on chromosome 19p13.3-p13.2. In addition to these two alleles some rare ones could be observed.

It is seen that concerning the average *C3* allele frequencies clear differences between the main human population groups are recognizable, though for some of them only few data are available hitherto and should be completed by further studies.

It should be mentioned only briefly, that also within these population groups the *C3* allele frequencies are varying more or less. Though the number of studies concerning this polymorphic serum protein system is yet relatively small in some of these population groups, it is remarkable that the *C3*F* allele is rather frequent only in the Europeans (0.192), in some distance followed by the Asians (0.80), whereas this allele is obviously less frequent in all the other population groups like Africans (0.064), Inuits (0.056), Oceanians (0.040) and Amerindians (0.010). Considering the essential immunobiological functions of the complement system it cannot be excluded that selectively acting forces might have contributed to this distribution differences. However, up to now it was not yet possible to propose a well-founded hypothesis concerning this, so that further research is necessary in order to explain the distribution pattern of the *C3* alleles.

It is seen from these figures, which are based on the data summarized by Roychoudhury and Nei (1988) and Bhasin et al. (1992), that the total Indian *C3*F* and *C3*S* allele frequencies do not differ from the mean frequen-cies of other Asian populations (0. 080), but are obviously different from the allele frequencies observed in European and other populations. Within India some regional variation is seen (North India - 0.097, Central India – 0.071, South India 0.064 and East India – 0.039), which, however, has to be ensured by further studies on population samples from because these sample sizes are quite low, and especially from West India, for which up to now no data are available (Bhasin and Walter 2001).

2.8. Orosomucoid (ORM) System

The orosomucoid system (ORM system) was described by Johnson et al. (1969). The physiological function of this protein, which is now frequently named as acid α_1-glycoprotein, is not yet cleared up completely. It is synthezised in the liver and seems to play a role in the binding of steroids and medicaments. A series of phenotypes are known, which are controlled by three autosomal co-dominant alleles: *ORM*1*, *ORM*2* and *ORM*3*. Here the new designa-tion of the alleles is used: *ORM*1* (= *ORM*F1*), *ORM*2* (= *ORM*S*), *ORM*3* (= *ORM*F2*). In addition to the standard phenotypes a number of rare genetic variants are known. Yuasa et al. (1986) assumed the existence of a second ORM locus, which, however, does not seem to be polymorphic.

It is seen that high frequencies of the *ORM*1* allele seem to be characteristic especially for Asiatic populations, in which it varies between 0.695 among Chinese (n=522) and 0.814 among Thais (n=369). This allele seems to be also rather frequent among Papuans from New Guinea. In the other population groups the frequencies of this allele are more or less lower. One has to consider, however, that in many regions the number of population studies is yet relatively low. It is noteworthy that the *ORM*3* allele is relatively frequent only among European populations, where it varies from 0.000 in Finns (n=49), Swedes (n=5454), English (n=555) and Hungarians (n=49) up to 0.049 in French (n=112). Another interesting observation is the high frequency of genetic variants among Asians. In Japanese (n=2058) e.g.

the sum of all rare ORM1 alleles amounts to 0.117! A plausible explanation for this is not yet possible.

Mastana et al. (1993), who analyzed the variability of OMR1 allele frequencies among Eurasian populations, found a distribution gradient, which is clearly correlated with the geographical longitude. Concerning the *OMR1*1* allele frequencies the correlation coefficient comes to r = +0.80 ($p<0.01$), and concerning the *ORM1*2* frequencies it comes to r = -0.84 ($p<0.01$). That means, that from west to east the *ORM1*1* allele frequencies are increasing, whereas the *ORM1*2* frequencies are decreasing. Mastana et al. (1993) suppose that apart from gene flow and genetic drift in this connection also selectively acting factors have to be taken into consideration, which, however, are yet quite unclear. It would be very interesting to follow up this speculation by further research.

As for India so far only two population samples have been typed for this polymorphic serum protein system. Among 50 individuals from Calcutta Johnson et al. (1969) observed the allele frequencies: *ORM1*1* = 0.440, *ORM1*2* = 0.560. These frequencies differ clearly from that reported for the others, but one can assume that they are due to chance and caused by the very small sample size. Another sample (n=740) has been typed by Mastana et al. (1993). They found the following allele frequencies: *ORM1*1* = 0.687, *ORM1*2* = 0.303, *ORM1*3* = 0.010, which do not differ obviously from those reported. Further population studies are necessary, however, in order to understand the distribution pattern of the ORM alleles in India (Bhasin and Walter 2001).

2.9. Properdin Factor B (BF) System

The genetic polymorphism of this serum protein system, called BF system, was described by Alper et al. (1972). This protein plays an important role concerning the activation mechanism of the complement. Apart from a number of rare variants up to now 14 different phenotypes are known, which are controlled by four autosomal co-dominant alleles: *BF*F*, *BF*S*, *BF*F1* and *BF*S1*. The gene locus lies on chromosome 6p21.3. Table 1 shows the worldwide distribution of the four BF alleles.

It has been observed that the highest *BF*F* allele frequencies are present among African populations, and it is very interesting to state, that especially the Sub-Saharan populations are characteristic by very high frequencies of this allele. It varies in these populations from 0.511 in Niger (n=103) up to 0.724 in Nigeria (n=98). Against that North African populations show much lower frequencies of this allele, e.g. Tunisians (0.281, n=375) or Algerians (0.321, n=996). Rather high *BF*F* allele frequencies are also observed among European (0.198), Asiatic (0.269) and Oceanic (0.171) populations, whereas Amerindians (0.022) and Inuits (0.010) are characteristic by very low frequencies of this allele. In these two populations groups the worldwide highest frequencies of the *BF*S* allele are existing. More or less marked population differences are also seen concerning the *BF*F1* and *BF*S1* allele frequencies.

For India up to now only rather few populations have been analyzed for the BF polymorphism, 12 from North India, one from South India, which were specified by Roychoudhury and Nei (1988) and Bhasin et al. (1992). It is noticeable, that in India the *BF*F* frequencies are higher and the *BF*S* frequencies are lower than in European and other Asian populations, and that the frequencies of *BF*F1* and *BF*S1* alleles are much lower. Further studies on more populations from all parts of the country are required, however, before a definite assess-ment of this striking observation would be possible.

Table 1: Worldwide distribution of four BF alleles.

Population	*Allele frequency*					
	n	*BF*S*	*BF*F*	*BF*S1*	*BF*F1*	*Others*
Europeans	27460	0.758	0.198	0.012	0.031	0.001
Asians	4074	0.674	0.269	0.053	0.003	0.001
Amerindians	1277	0.965	0.022	0.005	0.002	0.006
Inuits	368	0.989	0.010	0.000	0.001	0.000
Africans	3594	0.402	0.501	0.062	0.030	0.005
Oceanians	610	0.826	0.171	0.000	0.002	0.001
India	1148	0.642	0.350	0.006	0.002	0.000

2.10. α_2-HS-Glycoprotein (AHSG) System

This polymorphic serum protein system, also known as AHSG system, was described for the first time by Anderson and Anderson (1977). It is named AHSG system in memory of Heremans (H) and Schmid (S), who were intensively concerned with this protein (Cox et al. 1986). The function of this protein is not yet cleared up completely, but it seems to play an important role in connection with the phagocytosis by neutrophil leucocytes and monocytes. The AHSG system consists of three phenotypes, which are controlled by two autosomal co-dominant alleles: *AHSG*1* and *AHSG*2*. Some rare genetic variants are also known. The gene locus lies on chromosome 3q27-q29. The - rather difficult - typing method is described in detail by Boutin et al. (1985) and Cox et al. (1986). The highest frequencies of the *AHSG*1* allele are existing in the populations of Europe (0.687), Asia (0.718) and Africa (0.793), whereas this allele is obviously less frequent among Amerindians (0.300), Inuits (0.400) and Oceanians (0.296). It should mentioned here only briefly that within these population groups a more or less marked variability of the allele frequencies is present. So far this polymorphic serum protein system has not yet been studied on Indian populations (Bhasin and Walter 2001).

2.11. Plasminogen (PLG) System

The plasminogen system (PLG system) was discovered by Hobart (1979) and Raum et al. (1979). The plasminogen is synthezised in the liver and is the inactive stage of plasmin, which is a proteolytic enzyme with a broad spectrum of effects. This polymorphism consists of three phenotypes, which are controlled by two autosomal co-dominant alleles: *PLG*1* and *PLG*2*. Some rare variants are known. The gene locus lies on chromosome 6q26-q27. The high *PLG*1* allele frequencies are found in Asians (0.953), Amerindians (0.933) and Inuits (0.989), whereas this allele is obviously less frequent in Europeans (0.717) and Africans (0.703). Concerning the Asiatic data it is noteworthy, that highest frequencies of this allele are observed among those populations, which belong to the so-called "Mongoloid group". In the Thai population e.g. the *PLG*1* frequency comes to 0.987 (n=111), in Japanese (n=8896) and Koreans (n=149) to 0.955. The reasons for the high *PLG*1* frequencies in these Asiatic populations are unknown. Up to now no PLG allele frequency data are avaible for India (Bhasin and Walter 2001).

2.12. Factor 13 (F13 or F XIII) System

This polymorphic serum protein system (F13 system or F XIII system) comprises serum proteins, which play an important role in connection with the coagulation processes of the blood. The coagulation factor, being present in the plasma, consists of two subunits, called factor F13A and F13B. Both of them show a genetic polymorphism. This could be demonstrated by Board (1979, 1980). The F13A system consists of three phenotypes, which are controlled by two autosomal co-dominant alleles: *F13A*1* and *F13A*2*. The gene locus lies on chromosome 6p25-p24. The F13B system is characterized by six phenotypes, which are controlled by the alleles *F13B*1*, *F13B*2* and *F13B*3*. The gene for this system is located on chromosome 1q31-q32.1. In both the systems a number of genetic variants are known.

Concerning the factor 13A system it comes out from that in all so far tested populations the *F13A*1* allele is the most frequent one. No particular distribution differences are to be seen, however, even though the *F13A*1* frequencies are somewhat lower in Europeans (0.749) and Africans (0.755) (and also in the Australian Aborigines – 0.784) as compared to Asians (0.888), Oceanians (0.882), Ameridians (0.833), Papuans (0.826).

More interesting is the distribution pattern of the F13B allele frequencies as it is observed quite high frequeny of the *F13B*1* allele in Europeans (0.746), Oceanians (0.610). It is interesting to state that the low *F13B*1* frequencies among the Asiatic populations are restricted to those, which belong to the so-called "Mongoloid group". Thus e.g. in Chinese the *F13B*1* frequency was found to be 0.273 (n=375), in Japanese it comes to 0.287 (n=1148), whereas in the so-called "Caucasoid" populations the frequency of this allele is obviously higher, in Indians e.g. it amounts to 0.615 (n=313) and in Jordanians to 0.706 (n=124). Relatively low are the *F13B*1* frequencies among Amerindians (0.139), Inuits (0.263) and Africans (0.232). Clear differences are also seen concerning the *F13B*3* frequencies, which are considerably high only in Asians (0.606),

Amerindians (0.856) and Inuits (0.707). The *F13B*2* allele is relatively frequent only among Europeans. In Asia it is again found especially in the "Caucasoid" populations (Indians: 0.081; Jordanians: 0.125), whereas it is obviously less frequent in populations like Chinese (0.025) or Japanese (0.010), which belong to the so-called "Mongoloids". It would be very interesting to follow up this remarkable distribution pattern by further studies on populations of "Caucasoid" and "Mongoloid" affiliation. The *F13B*2* allele frequencies in Africa, extremely high (0.716). For India up to now only one study on the F13 system is known. The following allele frequencies could be observed: *F13B*1* = 0.615, *F13B*2* = 0.081, *F13B*3* = 0.299, and *F13B*Var* = 0.005(n=313); c.f. from Walter (1998).

2.13. Inter-α-Trypsin Inhibitor (ITI) System

This polymorphic serum protein system (ITI system) was discovered by Vogt and Cleve (1990). Thisprotein is synthezised in the liver and belongs to the protease inhibitors. The ITI system consists of six standard phenotypes, which are controlled by three autosomal co-dominant alleles: *ITI*1*, *ITI*2* and *ITI*3*. The gene locus lies on chromosome 9p21.2-p21.1. In addition to these three alleles some more were described, *ITI*4*, *ITI*5*, ITI*6, *ITI*7*, *ITI*Y* and *ITI*T*, which, however, are quite rare and seem to be restricted to a few populations only.

In all populations the most frequent ITI allele is the *ITI*1* (Inuits – 670, Europeans - 0614, Africans – 0.542) Asians – 0.526) followed - with the exception of Africans (0.130) - by the *ITI*2* allele Asians (0.443), Europeans (0.379) and Inuits (330). In Africans the *ITI*3* allele seems to be very frequent (0.317). The reasons for all these differences in the distribution of the ITI allele frequencies are still unclear. The *ITI*4* allele could be observed only in Japanese (0.002, n=765) and Korean (0.003, n=200) samples (Yuasa et al., 1991), the *ITI*5* allele only in Iranians (0.005, n=205), the *ITI*6* allele in Africans from the Ivory Coast (0.012, n=126) and the *ITI*7* allele in the sample from Cape Verde (0.008, n=265). Finally it should be mentioned briefly, that Harada et al. (1994) could identify two more ITI alleles, which seem to be restricted to Japanese (*ITI*Y*) and Thais (*ITI*T*), respectively. Up to now for India no studies concerning the ITI system have been reported.

3. RED CELL ENZYME POLYMORPHISMS

3.1. Adenosine Deaminase (ADA) System (E.C.3.5.4.4.)

Adenosine deaminase (ADA) is an amino-hydrolase which catalyses the deamination of adenosine to inosine. The enzyme is widely distributed in animal tissues. Adenosine deaminase shows an electrophoretic polymorphism genetically determined by the occurrence of two common alleles, *ADA*1* and *ADA*2*, at an autosomal locus; correspondingly there are 3 phenotypes: ADA 1, ADA 2 and ADA 2-1 (Spencer et al. 1968; Hopkinson et al. 1969; Tariverdian and Ritter 1969; Renninger and Bimboese 1970; Dissing and Knudsen 1970; Lamm 1971).

Several rare alleles have been reported (*ADA*1–ADA*9)* and they are present in heterozygous combinations of either *ADA*1* or *ADA*2* at the same locus (Hopkinson et al. 1969; Radam et al. 1974). There is also evidence for Null allele (s) which in homozygotes, who are grossly deficient in red cell and white cell ADA activity, is associated with severe combined immune-deficiency disease (Giblett et al. 1972; Dissing and Knudsen 1972; Hirschhorn et al. 1973; Chen et al. 1974; Meuwissen et al. 1975). Heterozygotes for such alleles are apparently healthy (Brinkmann et al. 1973; Chen et al. 1974). The ADA locus is assigned to the long arm of chromosome 20 (20q12-q13.11).

The *ADA*1* and *ADA*2* alleles have been observed with frequencies of about 0.95 and 0.05, respectively, in most European populations, *ADA*2* is relatively less frequent (about 0.02) in African Blacks, but more frequent (about 0.12) in Indians (Bhasin and Fuhrmann 1972). The presence of high *ADA*2* allele frequency suggest that this allele is of local origin, proliferating on account of some selective advantage in India. The frequencies are quite high for allele *ADA*1* among Tibetans (0.950), Chinese (varies from 0.939 to 0.957), Japanese (ranges from 0.969 to 0.972) whereas in Southeast Asia the frequencies of *ADA*1* are little low (vary from 0.885 among Malayans to 0.957 in Filipino) (Roychoudhury and Nei 1988, Walter 1998). The rare ADA allele encountered from India include *ADA*3* among Jats of Punjab (Singh et al. 1974b); *ADA*4* among Muslims of Delhi (Papiha et al. 1976), Ganchi and Anavil of Gujarat (Papiha et al. 1981) and *ADA*6* among Vadabalijas of Orissa (Reddy et al. 1989).

The frequency of *ADA*1* allele is 0.882 in various population groups in India, which is high among caste groups (0.897) as compared to rest of the ethnic groups among whom the frequencies are almost similar. The frequency of the *ADA*1* allele is high in North India (0.895) and low in East India (0.829). It is high among the speakers of Mon Khmer group of Austro-Asiatic, Bhotia and Himalayan groups of Tibeto-Chinese and Pahari group of Indo-European languages for the Himalayan region, where most of the populations are with Mongoloid admixtures in varying degrees, whereas among speakers of Indo-European and Dravidian languages the frequencies are low (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

3.2. Adenylate Kinase (AK) System (E.C.2.7.4.3)

Adenylate kinase, also called ATP: AMP phosphotransferase occurs in red cells as well as in muscles and other tissues. It catalyses the reversible reaction -

Adenosine diphosphate $\rightleftharpoons$ Adenosine triphosphate+Adenosine monophosphate (2ADP ATP + AMP)

Three different groups of isozymes of adenylate kinase, Adenylate kinase 1, Adenylate kinase 2, (Khoo and Russell 1972) and Anenylate kinase 3, (Wilson et al. 1976) determined by three separate gene loci *AK1*1, AK*2* and *AK*3* have been identified. Genetically determined polymorphism of Adenylate kinase 1 isozymes in red cells was first demonstrated by Fildes and Harris (1966) and three distinct phenotypes AK1 1, AK1 2-1 and AK1 2 could be found by starch gel electrophoresis. They showed with the help of family and mother/child studies these to be genetically determined by two alleles *AK1*1* and *AK1*2*. A few rare variants of this system are reported (AK1 3-1 by Bowman et al. 1967; AK1 4-1 by Rapley et al. 1967; AK1 5-1 by Santachiara-Benerecetti et al. 1972a). Linkages between AK, nail patella and ABO loci have been reported (Rapley et al. 1967; Weitkamp et al. 1969; Wille and Ritter 1969; Wendt et al. 1971). The locus for the AK gene is assigned to the long arm of chromosome 9 (9q34.1).

Evidence for a rare allele resulting in gross deficiency of Adenylate kinase 1 activity associated with chronic haemolytic anemia in the homozygote has been provided (Szeinberg et al. 1969; Boivin et al. 1971), and a partial deficiency of red cell adenylate kinase possibly due to heterozygosity for the same or a similar allele has been described (Singer and Brock 1971).

*AK1*1* is the most frequent allele in all the populations studied. In most of the European populations *AK1*1* occurs with frequencies between 0.86 and 0.98, in Mongoloids this allele varies between 0.98 and 1.000 (Mourant et al. 1976a). From Indian region, *AK1*1* allele frequency ranges from 0.88 to 0.92. Among Africans and Australian Aborigines this allele appears to be very uncommon (Bhasin and Fuhrmann 1972). The other alleles *AK1*3*, *AK1*4*, *AK1*5* have been reported indifferent populations but they are very rare (Walter 1998).

In Indian populations the frequency of allele *AK1*1* is 0.924 (varies from 0.795 to 1.000). The frequency is high in scheduled tribes (0.943) and low among scheduled caste groups (0.907). Among the population groups with Mongoloid affinities the frequency is high from East India. The frequency of *AK1*1* allele in North, West and East India is almost similar. In the Himalayan region allele *AK1*1* is high in Eastern region (0.954). Among the speakers of different languages, the frequency is high in Tibeto-Chinese language family (0.976) than Dravidian and Indo-European family (0.919 and 0.918, respectively) (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

3.3. Red Cell Acid Phosphatase (ACP1) System (E.C.3.1.3.2)

Acid phosphatase is a phosphohydrolase and phosphotransferase but the exact functional role of the enzyme is unknown. A genetic polymorphism of this enzyme in red cells was first demonstrated by Hopkinson et al. (1963). Five different phenotypes could be seen after starch gel electrophoresis, referred to as ACP1 A, ACP1 BA, ACP1 B, ACP1 CA and ACP1 CB. Family studies suggested that three autosomal alleles *ACP1*R*, *ACP1*B* and *ACP1*C* controlled these patterns. The sixth and rare phenotype C was reported later by Lai et al. (1964). Three rare alleles (*ACP1*R*, *ACP1*D* and *ACP1*0*) have been described by Giblett and Scott (1965), Karp and Sutton (1967) and Herbich et al. (1970). The ACP locus is assigned to the short arm of chromosome 2 (2p25).

Evidence for probable influence of red cell acid phosphatase phenotypes on the fitness of individuals, depending on their genotype at other loci, has been advanced by Bottini et al. (1971) and Palmarino et al. (1975). Bottini et al. (1971) described an association between favism and acid phosphatase phenotypes in G-6-PD deficient male subjects. The data suggested that the susceptibility of these subjects to hemolysis is highest for the ACP1 A and ACP1 CA phenotypes, intermediate for ACP1 BA and ACP1 BC, and lowest for ACP1 B phenotypes. Palmarino et al. (1975) reported that their study suggests an interaction between thalassaemia and acid phosphatase mediated by the habit of eating *Vicia fava;* this interaction conditions the susceptibility to hemolytic favism in G-6-PD deficient subjects, whereas Saha and Patgunarajah (1981) found that the phenotypic association of acid phosphatase was observed only in case of G-6-PD deficiency with favism in the Italian sample. There was a poor positive correlation of red cell acid phsophatase and G-6-PD activities ($r = 0.13$). This differential selective adaptability of different genes in different populations of the world in response to different environmental conditions such as temperature, humidity, radiation, infective diseases etc. may be responsible for the conflicting results of the association of G-6-PD deficiency and other abnormalhaemoglobins with a history of malarial mortality and morbidity.

Walter (1976) reported the effects of selectively acting ecological factors such as mean annual temperature on acid phosphatase gene. In view of the marked quantiative differences in the enzyme activity of the different phenotypes of erythrocyte acid phosphatase (Berg et al. 1974; Dissing and Svensmark, 1976; Eze et al. 1974; Spencer et al. 1964a) the role of differential selection in bringing about the existing variability of this red cell enzyme in various populations from different ecosystems could have been substantial.

The red cell acid phosphatase alleles *ACP1*A, ACP1*B, ACP1*C* and *ACP1*R.* occur with polymorphic frequencies in various populations. Among Europeans the *ACP1*A* allele varies from 0.26 to 0.40 and that of *ACP1*B* from 0.56 to 0.72, in Far East Asian populations the frequency of allele *ACP1*A* ranges in between 0.20 and 0.28 and that of *ACP1*B* from 0.72 to 0.80, in Southeast Asian populations frequency for *ACP1*A* ranges from 0.11 to 0.33 and for *ACP1*B* from 0.66 to 0.86, whereas in Africans (Blacks) *ACP1*A* varies from 0.11 to 0.21 and *ACP1*B* from 0.56 to 0.85 (Bhasin and Fuhrmann 1972). Considering the frequency of red cell acid phsophatase alleles the most notable trend is the relative high frequency of allele *ACP1*C* in European populations. This allele was therefore regarded as 'Caucasian' by Scott et al. (1966). Its occurrence in other populations was thought to be due to Caucasian admixture (Tashian et al. 1967). Allele *ACP1*R* is common (0.02 to 0.24) in Blacks, it has not been observed in Europeans (Walter, 1998).

A number of other variant phenotypes due to rare alleles *e.g. ACP1*D*, (Lamm, 1970) and *ACP1*E* (Sörensen, 1975), *ACP1*F, ACP1*G* (Nelson et al. 1984), *ACP*TIC-1,* (Yoshihara and Mohrenweiser 1980) and *ACP*GUA-1* (Mohrenweiser and Novotony 1982) have also been identified in population studies, but they are infrequent and so far have been detected only as heterozygotes with one or other of the polymorphic alleles of the system. There is also evidence for rare "null" alleles *ACP*0*; the heterozygote carriers are healthy (Herbich et al. 1970).

The frequency of allele *ACP1*B* is higher (0.756) than *ACP1*A* (0.242) whereas *ACP1*C* occurs in very low frequency (0.002) in India. The frequency of allele *ACP1*C* is almost similar and quite low in most of the studies reported and *ACP1*B* frequency is low in scheduled caste and scheduled tribe groups as compared to others. The allele *ACP1*C* is present in the various groups reported from Himalayan region and *ACP1*A* is present in low frequency in the Western region (0.225). The frequency of allele *ACP1*A* is low in Tibeto-Chinese language speakers of Mongoloid affinities and in Munda group (Austro-Asiatic family) and Dravidian group of languages speakers who are mostly tribals as compared to the speakers of Indo-European languages–Central group (0.298) and Bihari (0.250) (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

3.4. Phosphoglucomutase (PGM1) System (E.C.2.7.5.1)

Phosphoglucomutase (PGM1) catalyses the interconversion of glucose-1-phosphate and glucose-6-phosphate. It is an important enzyme in glycogen mobilization and is found in most

body tissues. Spencer et al. (1964) identified a total of seven zones (a to g) of enzyme activity-after the starch gel electrophoresis of haemolysates. The three fast moving zones e, f and g were found in all individual samples tested, whereas zones a, b, c and d varied among them. Family studies indicated that three different patterns PGM1 1-1, PGM1 2-2, PGM1 2-1 are controlled by two autosomal alleles *PGM1*1* and *PGM1*2* (Spencer et al. 1964b). In addition to the two common alleles many rare alleles have been reported (Hopkinson and Harris 1966; Harris et al. 1968; Fielder and Pettenkofer 1968; Saha et al. 1974; Blake and Omoto 1975; Horai 1975). A complete deficiency of PGM1 isozyme activity has been reported (Fielder and Pettenkofer 1969) and attributed to homozygosity for a null allele at the PGM1 locus.

By isoelectric focusing (IEF) phosphoglucomutase locus 1 was shown to be controlled by four suballeles

*PGM1*1A (PGM1*1 +, PGM1*a1, PGM1*1a* and *PGM1*1S*);
*PGM1*1B (PGM1*1 –, PGM1*a3, PGM1*1b* and *PGM1*1F*);
*PGM1*2A (PGM1* 2+, PGM1*a2, PGM1*2a* and *PGM1*2S*); *and*
*PGM1*2B (PGM1* 2–, PGM1*a4, PGM1*2b* and *PGM1*2F*);

depending on whether the focusing was towards the anodal or cathodal side of the focused gel (Bark et al. 1976; Kühnl and Spielmann 1977; Kühnl et al. 1978; Prokop and Göhler 1986). The presence of *PGM1*1* in both human and other primates suggests that this may be an ancestral allele in man from which the other three common alleles have evolved by mutation. Takahashi et al. (1982) extended the four-allele phylogeny to an eight-allele one after the discovery of *PGM1*3* and *PGM1*8* subtypes. Dykes et al. (1985) proposed the classification of the rare variants of the PGM1 locus. It appears that the PGM1 locus is controlled by four common and numerous rare alleles providing us with an extensive array of phenotypic variations suitable for detailed population genetic studies in man. Further, the presence of rare 'Null' and thermostability alleles at the locus in man overcome the scope of variability of the locus (Scozzari et al. 1984; Ward et al. 1985).

The fast moving zones e, f and g were found to be controlled by genes at a separate locus called PGM2 (Hopkinson and Harris 1965, 1966). Only very few variants have been reported at this locus and the common type is invariably PGM2 1-1. The presence of a third locus PGM3, for phosphoglucomutase has been demonstrated in tissues other than red cells (Hopkinson and Harris 1968). The locus for PGM1 is assigned to short arm of chromosome 1 (1p22.1), for PGM2 to chromosome 4 (4p14-q12) and for PGM3 to chromosome 6 (6q12).

The two common alleles *PGM1*1* and *PGM1*2* have been observed with appreciable frequency in every major ethnic group, out of which the frequency of *PGM1*1* is more as observed among Europeans - 0.70 to 0.86; Africans - 0.76 to 0.84; Southwest Asians - 0.60 to 0.79; East Asians - 0.73 to 0.77; Southeast Asians - 0.682 to 0.782; Tibetans - 0.705 to 0.732; Bhutanese - 0.770. Numerous other variant phenotypes attributable to rare *PGM1** alleles in heterozygous combination with either *PGM1*1* or *PGM1*2* have been indentified. *PGM1*7* is perhaps the most frequent of the rare *PGM1** alleles in India region; the other rare alleles observed are *PGM1*3*, *PGM1*5* and *PGM1*6*.

Phosphoglucomutase locus 1 is shown by isoelectric focusing to be determined by four common alleles (*PGM1*1A*, *PGM1*1B*, *PGM1*2A*, *PGM1*2B*). An appreciable heterogeneity is observed in various studies reported on subtypes of *PGM1**. The frequency of *PGM1*1A* varied more widely in the Mongoloid (0.53 to 0.71) and Black (0.48 to 0.73) populations than in the Caucasians (0.61 to 0.65). The variation of *PGM1*1B* is also larger in the former two groups (0.10 to 0.16 in Mongoloids and 0.11 to 0.25 in Blacks) than the Caucasians (0.11 to 0.14). The frequency of *PGM1*2A* also varied more among the Mongoloids (0.05 to 0.17) and Blacks (0.10 to 0.16) than among the Caucasians (0.17 to 0.24). The *PGM1*2B* varied within a narrower range among the Caucasians (0.04 to 0.08) and Blacks (0.03 to 0.06) than in the Mongoloids (0.04 to 0.14). The mean frequency of *PGM1*1A* was observed almost similar in the three races (0.631 ± 0.005, 0.637 ± 0.012 and 0.656 ± 0.021, respectively) while the frequency of *PGM1*2A* was significantly higher in the Caucasians (0.196 ± 0.013) compared to that in the Blacks (0.155 ± 0.011) and Mongoloids (0.137 ± 0.012). The Blacks had a higher average frequency of *PGM1*1B* (0.169 ± 0.021) compared to the Caucasians and Mongoloids (0.114 ± 0.010 and 0.119 ± 0.009, respectively). The Mongoloids are characterised by a low frequency of *PGM1*2B* (0.023 ± 0.008) compared to

Caucasians (0.054 ± 0.006) and Blacks (0.034 ± 0.006) studied by Saha (1988b).

The *PGM1*1* allele frequency is 0.700 in India (varies from 0.442 to 0.950), is low in scheduled tribe (0.690) and high in scheduled caste (0.713) groups. The frequency is quite low in Islands (0.657), high in Central India (0.719) and again low in Eastern Himalayan region (0.691). The distribution of this allele is similar among speakers of different languages (varies from 0.695 to 0.703) except those of Austro-Asiatic family among whom the frequency is low (0.669). The *PGM1*1A* frequency is low among scheduled tribe as compared to other ethnic groups. The frequency is high from the states of West Bengal (0.726), Karnataka (0.733) and Andhra Pradesh (0.745), whereas from North India the frequency is low (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

3.5. 6-Phosphogluconate Dehydrogenase (6-PGD) System (E.C.1.1.1.43)

The oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate in the hexosemonophosphate (HMP) shunt is catalysed by the enzyme 6-phosphogluconate dehydrogenase (6-PGD). Fildes and Parr (1963) described the inherited variation in the enzyme and three common electrophoretic variants PGD A, PGD C and PGD AC were observed in haemolysates and white blood cells. Family studies have shown that these variants are controlled by two codominant autosomal alleles *PGD*A* and *PGD*C* (Parr 1966; Bowman et al. 1966; Parr and Fitch 1967; Carter et al. 1968). Further, a number of rare variants have been reported at the 6-PGD locus. Some of these variants are not recognizable by electrophoresis but by a decrease in the enzyme activity, as compared to the normal.

The 6-PGD locus is assigned to chromosome 1(1p36.3–p36.13). About twenty two rare alleles are reported at this locus. These include *PGD*Hackney*, *PGD*Friendship*, *PGD*Richmond* and *PGD*Whitechapel* (Parr, 1966 and Davidson 1967); *PGD*Thailand* (Tuchinda et al. 1968); *PGD*Elcho* (Kirk et al. 1969); *PGD*Freiburg* (Tariverdian et al. 1970); *PGD*Singapore* (Blake et al. 1973); *PGD*Wantoat*, *PGD*Canberra*, *PGD*Kadar*, *PGD*Caspian*, *PGD*Bombay* and *PGD*Natal* (Blake et al. 1974); *PGD*Korea* (Benkmann et al. 1986) and *PGD*Mediterranean* (Nevo, 1989).

The variant alleles though generally rare occasionally reach frequencies greater than 0.01 in isolated populations for example *PGD*Elcho* in Australian Aborigines (Blake and Kirk 1969) and *PGD*Kadar* in tribal group from South India (Blake et al. 1974). Two rare silent variant alleles (*PGD*O* and *PGD*W*) associated with marked enzyme deficiency have been identified in heterozygous combinations with common alleles *PGD*A* and *PGD*C* (Parr and Fitch 1967). These heterozygotes were healthy and so too was the homozygote for the *PGD*W* allele.

Among Indian populations the rare variants reported are PGD Richmond (RA), PGD Friendship (FA), PGD A-Waltair, PGD Hackney (HA), PGD A-Kadar (AK), PGD C-Kadar (CK) and PGD Kadar (K).

The frequency of *PGD*A* is quite high (more than 0.90 in most of the populations) as compared to *PGD*C*. The frequency of *PGD*A* in most European populations ranges from 0.95 to 0.98. In South west Asian populations the frequency is low in Arbas, but in general it is around 0.95. In Nepal and Bhutan *PGD*A* frequency is 0.914 and 0.770, respectively. Among populations of Southeast Asia and East Asia the frequencies are around 0.95 and 0.92, respectively. The frequency of *PGD*A* varies from 0.85 to 0.97 among Africans and from 0.94 to 0.96 in Australian Aborigines (Bhasin 2009; Bhasin et al. 1994).

The frequency of allele *PGD*A* is observed 0.959 among Indian population (varies from 0.754 to 1.000). High frequency of this allele is observed among scheduled castes (0.985) as compared to other ethnic groups. However from East and South India zones, the frequency of *PGD*A* is low among scheduled tribes. The frequency of *PGD*A* is high in the West and South India zones and low in East India zone. The pattern of distribution of allele *PGD*A* among speakers of different languages shows low frequency in Tibeto-Chinese and Pahari group of Indo-European languages in the Himalayan region and then it increases in the speakers of Indo-European (0.959) and Dravidian (0.973) languages (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

3.6. Esterase D (ESD) System (E.C.3.1.1.1)

Of the four biochemically and genetically different esterases known in human red cells-A,

B, C (Tashian 1961, 1969) and D (Hopkinson et al. 1973) only the latter (ESD) has been found to exhibit a genetic polymorphism in man. Three different commonly occurring electrophoretic types were identified and designated ESD 1-1, ESD 2-2 and ESD 2-1. Family studies suggest that these are determined by two alleles *ESD*1* and *ESD*2* at an autosomal locus. The enzyme has been detected in all human tissues examined (Hopkinson et al., 1973), however its physiological role is not yet known (Cotes et al. 1975). At least 17 more alleles have been identified in addition to two common alleles. These include *ESD*3*, *ESD*4*, *ESD*Momelodi*, *ESD*3Negrito*, *ESD*3.1*, *ESD*5*, *ESD*6*, *ESD*7a*, *ESD*Düsseldorf*, *ESD*1-D*, *ESD*Düsseldorf-ESD*Düs2*, *ESD*Copenhagen*, *ESD* Yamaguchi*, *ESD*Berlin*, *ESD*Korfu*, *ESD*11*, *ESD*Lisbon* (after Munier et al. 1988). In addition, the occurrence of a silent or null allele *ESD*O* has also been reported (Marks et al. 1977). Esterase D (ESD) and the S-formylglutathione hydrolase (FGH) polymorphisms are identical as concluded by Apeshiotis and Bender (1986) from the analyses of families, populations and somatic cell hybrids. The locus for ESD is assigned to chromosome 13 (13q14.1–q14.2).

The distribution of the common allele *ESD*1*, varies from 0.365 in Parakana of Brazil to 1.000 in Australian Aborigines. *ESD*1* occurs with a frequency of about 0.90 in Europeans followed by Southwest Asians (around 0.80), populations from Indian Region (about 0.75), Southeast Asians (about 0.70) and East Asians (0.65). Among Tibetans, the frequency varies from 0.59 to 0.80 (Mourant et al., 1976a; Roychoudhury and Nei 1988; Walter 1998).

In populations of India, the frequency of *ESD*1* allele is 0.729 (varies from 0.418 to 0.978). The frequency is high in North India (0.775) followed by West, Central, South and East India and is quite low from Islands (0.565). The frequency is high in Himalayan region (Western as compared to Eastern region) followed by Indus-Ganga-Brahmaputra plains as compared to peninsular region. Among ethnic groups, the frequency is low among scheduled tribes (0.690) as compared to other groups. The frequency is high (0.758) among the speakers of Indo-European language as compared to speakers of other languages (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

3.7. Glucose-6-Phosphate Dehydrogenase (G-6-PD) System (E.C.1.1.1.49)

Glucose-6-phosphate dehydrogenase (G-6-PD) enzyme is necessary as a catalyst in a biological oxidation-reduction reaction of glucose-6-phosphate–one of the stages in the metabolism of carbohydrates. The G-6-PD deficiency disease was discovered when a number of Americans of African and Asian descent were treated with certain antimalarial drugs particularly primaquine, which produced a mild haemolysis in these individuals (Carson et al. 1956). Investigations showed them to be deficient in the red cell enzyme G-6-PD. A number of other drugs chemically related to primaquine produce haemolysis when given to individuals deficient in G-6-PD (WHO 1967). Favism, a haemolytic condition produced by eating fava beans (*Vicia fava*) is observed among populations living in the Mediterranean area and is believed to be connected with G-6-PD deficiency. The G-6-PD deficiency in red cells is inherited as an X-linked trait (chromosome location Xq28). Heterozygous females are usually intermediate between normal individuals and those clearly G-6-PD deficient.

Two common types referred to as A and B could be demon strated by electrophoresis. The commonest allele in all populations is *G6PD*B*. In Africans two other alleles *G6PD*A+* and *G6PD*A–* are also relatively common each with allele frequencies between 0.01 and 0.25 in different populations. In Mediterranean countries and the Middle East another allele *G6PD* Mediterranean* is relatively common. Certain electrophoretic variants also occur in Southeast Asia (*G6PD*Canton*) and in Greece (*G6PD* Athens*).

Investigations of enzyme in different human populations have shown many variants—more than 300 different variants have been described on the basis of their biochemical properties (Luzzatto and Mehta 1989; Beutler 1990) and most of them are relatively rare, but some have appreciable frequencies in certain localised populations. So far seven different G-6-PD variants namely - *G6PD* Andhra Pradesh* (Rattazzi 1966), *G6PD*Cutch* (Goshar 1979), *G6PD* Jammu* (Beutler 1975), *G6PD* Kalayan* (Ishwad and Naik 1984), *G6PD*Kerala* (Azevedo et al. 1968), *G6PD*Porbandar* (Cayani et al. 1977; Goshar 1979) and *G6PD*West Bengal* (Azevedo et al. 1968) have been reported from

India. With the cloning and sequencing of G-6-PD the variants that were thought to be different have proven to be identical, and those that were thought to be the same are now seen to be heterogenous (Martini et al., 1986; Persico et al. 1986a, b; Takizawa et al. 1986 and Yoshida and Takizawa 1986).

Most of the studies on G-6-PD published prior to the WHO Report (1967) were based on investigations carried out on patients in hospitals, manifesting clinical conditions such as haemoglobinuria, neonatal jaundice, drug-induced haemolytic anaemia etc. It has been estimated that approximately hundred million people suffer from G-6-PD deficiency in different parts of world (Azevedo et al. 1968; WHO 1967).

The Rhesus and ABO blood groups have been analysed in G-6-PD deficient and non-deficient samples. The frequency of Rhesus negatives was observed low among Sardinians and Congolese Bantus, both of whom show very high frequency of primaquine sensitivity (Sonnet and Michaux, 1960). In the distribution of B and O blood groups, Tarlov et al. (1962) observed relative rarity of B group in deficients. However, Baxi et al. (1963) and Jolly et al. (1972) failed to observe such differences.

Prenatal selection and foetal development disturbances are reported in carriers of G-6-PD deficiency by Toncheva and Tzoneva (1985) and they observed that the incidence of spontaneous abortions in first trimester is higher (21.7 per cent) in the women of heterozygous carriers of G-6-PD deficiency as compared to control group (9.3 per cent).

Limited information on the distribution of G-6-PD phenotypes is available among the population groups reported from different areas. It is believed that red cell G-6-PD deficiency is one of the important markers to explore the eco- and pharmacogenetic aspects of a population, due to its association with past malarial incidence.

G-6-PD deficiency was mainly found in populations originating from tropical and sub-tropical areas of the world. The geographic distribution was similar to that of falciparum malaria and suggested that G-6-PD deficiency similar to the sickling trait owed its distribution to selection by this malarial organism. Evidence related to a correlation of the frequencies of the sickling gene and that of A-type of G-6-PD deficiency exists in African countries and that between β-Thalassemia and the Mediterranean type of G-6-PD deficiency in Sardinia.

The deficiency of G-6-PD is found in a belt extending from Mediterranean area through Southwest Asia and India to South east Asia. The *G6PD*def* is very much prevalent in Saudi Arabia (varies from 0.07 to 0.44). Perhaps the highest frequency of deficiency recorded is among Shia of Al Qatif, Saudi Arabia (0.44), whereas the incidence in other Southwest Asian countries ranges from 0 to 0.21. From East Asian populations the frequency of *G6PD*def* is low (0.01 to 0.05). Among Khmer population from Vietnam (South east Asia) the frequency of *G6PD*def* is highest (0.15 to 0.35) and in Central and North-East Thailand the incidence is 0.11 to 0.17, but in most populations of Southeast Asian region the frequencies are less than 0.10. In the Indian region, it is around 0.19 (Mourant et al. 1976a).

The frequency of *G6PD*def* is 0.045 (varies from complete absence to 0.271) among Indian populations and it is high among scheduled tribes (0.055) as compared to other ethnic groups. The frequency is comparatively higher in North and West India zones, which indicates considerable stability of this allele in these areas, whereas in South India it is uniformly low except in Andhra Pradesh and Tamil Nadu and from East India the studies are too few to evaluate. Among the speakers of different languages, the frequencies are high in Mon Khmer group, North East Frontier group, Bodo group and Pahari group from Himalayan region and low among the speakers of Dravidian languages. The studies available from different ecological settings are not sufficient as yet to evaluate the distribution of this genetic marker in India, especially in connection with prevalence of malaria (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

Less Investigated Red Cell Enzyme Polymorphisms

The so far less investigated red cell enzyme polymorphisms are the following: *phosphoglycolate phosphatase system* (*PGP system*), the *uridin monophosphate kinase system* (*UMPK system*), the δ-*aminolevulinate dehydratase system* (*ALDAH system*), the *phospho-hexoi-somerase system* (*PGI system*), the *superoxid dismutase system* (*SOD system*), the *phospho-glycerat kinase system* (*PGK system*), the *carbonic anhydrase system* (*CA system*), and the *lactate deydrogenase system* (*LDH system*). One of the reasons, why these polymorphic red cell enzyme polymorphisms

have not yet been studied to such a great extent as the others can also be seen in the fact that their typing is rather difficult and requires, too, special reagents and equipments.

3. 8. Phosphoglycolate Phosphatase (PGP) System (E.C.3.1.3.18)

This polymorphic system, the PGP system, was discovered by Barker and Hopkinson (1978). This enzyme plays an important role with regard to the oxygen transport. Six electrophoretically demonstrable phenotypes are known, which are controlled by three autosomal co-dominant alleles: *PGP*1*, *PGP*2*, *PGP*3*. The gene locus lies on chromosome 16p13.3.

In all so far investigated human populations the *PGP*1* allele is the most frequent one. It is remarkable that in Africans (1.000), Australian Aborigines (1.000) and Papuans (1.000), from New Guinea only this allele seems to be present followed by Oceanians (0.995), Inuits (0.990), Asians (0.954), Europeans (0.887) and the lowest frequency of the *PGP*1* allele is seen among the Amerindians (0.719). On the other hand Amerindians is marked by rather high frequencies (0.276) of the *PGP*2* allele, which is - with the exception of the Europeans (0.085) - quite rare or even completely absent in all the other populations. Concerning Asia it is interesting to state, that the *PGP*2* allele seems to be more frequent among the populations of Western Asia (e.g. Turks: 0.018, n=110; Iranians: 0.065, n=200) than among thosefrom the eastern and southeastern parts of this continent, where it is either quite rare (e.g. in Malaysia: 0.005, n=109) or even completely absent (Indonesia, Thailand, China, Korea). The *PGP*3* allele seems to be relatively frequent only in Europeans (0.028). The existence of this allele among Oceanians, where it was found in the populations of Guam (0.025, n=100) and Samoa (0.004, n=130), was explained by "European admixture" (Blake and Hayes 1980). The reasons for these partially striking differences in the distribution of the PGP frequencies are unknown. Up to now only two Indian population samples have been typed for this polymorphic enzyme system. Among Indians from Bombay (n=120) the *PGP*1* allele frequency was found to be 0.954, among Indians from Malaysia (n=116) the *PGP*1* allele frequency came to 0.965. The corresponding *PGP*2* frequencies amount to 0.046 and 0.035, respectively (Blake and Hayes 1980). These frequencies correspond to those observed among European and Asiatic populations (Bhasin and Walter 2001).

3.9. Uridine Monophosphate Kinase (UMPK) System (E.C.2.7.4)

This enzyme belongs to the transferases and catalyzes the transformation of uridine monophosphate and ATP into uridine diphospate and ATP. The polymorphic nature of this enzyme system, the UMPK system, was described by Giblett et al. (1974). The hitherto known phenotypes can be explained by the assumption of three autosomal co-dominant alleles: *UMPK*1*, *UMPK*2*, *UMPK*3*. The gene locus lies on chromosome 1p32.

According to the figures presented in table 8.2 the *UMPK*1* allele is obviously the most frequent one in all populations. In Africans it seems to be the only UMPK allele. Whereas among European populations the variability of *UMPK*1* (0.965) and *UMPK*2* (0.035) allele frequencies is quite low, it seems to be more pronounced in Asia, as the *UMPK*2* (0.097) frequencies are e.g. obviously higher in Malayans (0.149; n=168), Chinese (0.120, n=125) and Negritoes from Luzon (0.345; n=129) than in Indians (0.058; n=121) and Japanese (0.053; n=635).

Of considerable interest, however, are the very high *UMPK*3* allele frequencies among Amerindians (0.124) and Inuits (0.200). Though up to now only very few Amerindian and Inuit samples were tested for the UMPK system, it could be observed, that in all of them the frequency of this allele is rather high, so that one can assume, that the *UMPK*3* allele seems to be typical for Amerindians as well as for Inuits. One cannot exclude that this UMPK allele came into existence by mutation after the immigration of the ancestors of the Amerindians and Inuits, respectively, from Asia to America - via the Bering Street - and could spread here (Bhasin and Walter 2001).

3.10. δ-Aminolevulinate Dehydratase (ALADH) System (E.C.4.2.1.24)

The δ-aminolevulinate dehydratase plays an important role in the biosynthesis of the haem. The polymorphism of the δ-aminolevulinate dehydratase, the ALADH system, was discovered

by Battistuzzi et al. (1981). It consists of three phenotypes, which are controlled by two autosomal co-dominant alleles: *ALADH*1* and *ALADH*2*. The gene locus lies on chromosome 9q32-q34.

Up to now, however, only few populations have been tested for this polymorphic red rell enzyme system, most of them from Europe and Asia. Among Africans only *ALADH*1* allele frequency is reported (1.000) followed by Amerindians (0.986), Europeans (0.917) and Asians (0.886) (Bhasin and Walter 2001).

3.11. Phosphoglucoseisomerase (PGI) System (E.C.5.3.1.9)

The phosphoglucoisomerase (PGI) system (also known as phosphohexoisomerase system) was described by Detter et al. (1968). This enzyme catalyzes the transformation of fructose-6-phosphate into glucose-6-phosphate. Apart from the PGI 1 phenotype, which is predominant in all hitherto typed populations, numerous genetic variants are known, which are caused by at leat 10 different alleles. The gene locus lies on chromosome 19q13.1. As in the most populations the frequency of the *PGI*1* allele amounts to 1.000 or is at least very frequent (more than 0.995) the PGI system is strictly speaking no polymorphic one. The *PGI*2* allele was observed in some Asiatic populations, e.g. in Thais (0.001; n=441) and Chinese from Singapore (0.001; n=378). It was also discovered in an isolated population from the northern highlands of New Guinea (0.033; n = 272). It seems that the *PGI*3* allele has a greater distribution, because it was found in European, Asiatic and African populations. However, the observed allele frequencies are everywhere very low and do not exceed 0.004 as e.g. in Italians from Bologna (n=274). In Asia this allele seems to be completely absent in most of the so far tested populations. Low frequencies of it were found among the Turkomans from Iran (0.010; n=155) and among Muslims from Bangla Desh (0.010; n=200). In India the frequency of the *PGI*3* allele seems to be somewhat higher; it varies between 0.002 in a sample from Andhra Pradesh (n=211) up to 0.008 in a sample from Madhya Pradesh (n=338). This allele could be observed also in a Hutu sample from Burundi (Africa). The alleles *PGI*4 - PGI*9* were observed in various populations of Asia (India, Nepal, Bangla Desh, Thailand, Japan), but the frequencies are very low (<0.005). Further rare PGI alleles were also found in some African populations, e.g. in the Sandawe and Nyaturu from Tanzania, and in South American Indians, e.g. the Cayapo and Wapishana from Brasil. No rare PGI alleles could be observed until now in the Australian Aborigines, in the populations of the Pacific region, in the North and Central American Indians and in the Inuits.

It is difficult to explain the distribution patterns of the various PGI alleles, which most likely came into existence by independent mutations. Anyway it is remarkable that the *PGI*3* allele seems to be more frequent in European and Asiatic populations than in all the others (Bhasin and Walter 2001).

3.12. Superoxide Dismutase (SOD) System (E.C.1.15.1.1)

This enzyme is existing in two molecular types: SOD A and SOD B. Beckman et al. (1973) could show, that SOD B is absent in erythrocytes. The biological function of this enzyme can be seen in its ability to protect the organisms from free radicals. The genetic polymorphism of the SOD A system was discovered by Brewer (1967). Three electrophoretically demonstrable phenotypes are known, which are controlled by two autosomal co-dominant alleles: *SOD A*1* and *SOD A*2*. The gene locus lies on chromosome 21q22.1.

The hitherto performed population studies reveal, that in almost all human populations the frequency of the *SOD A*1* allele is extremely high, and in many cases it comes even to 1.000. The *SOD A*2* allele was found only sporadically, especially in European populations, and here above all in Swedes and Finns. In Finland the *SOD A*2* allele frequencies vary from 0.002 in the south (n=143) up to 0.024 in the north (n=127), in Sweden from 0.002 (n=2366) up to 0.025 (n=1710). The *SOD A*2* allele was also observed in Finnish and Swedish Saami: 0.007 (n=1221) and 0.002 (n=210), respectively. It was suggested that these populations acquired the *SOD A*2* allele by gene-flow from the Finnish or Swedish side, respectively. In other European populations this allele is either completely absent or very rare. The highest frequency of the *SOD A*2* allele within Europe was observed among the population of the Orkney Islands (0.015, n=94). According to Beckman and Pakarinen (1973) this can be explained by the Scandinavian origin of this population. In non-European populations this

allele was also observed here and there, e.g. in Asians (Iraqis: 0.003, n=320; Iranian Turkomans: 0.013, n=155); Filipinos: 0.003, n=146; Japanese: 0.0001, n=5000), and in Africans from Central Africa (0.005, n=92). In Amerindians, Inuits as well as in the populations of New Guinea, Melanesia, Micronesia and Polynesia up to now the *SOD A*2* allele was never observed.

According to Beckman and Pakarinen (1973) it is unlikely, that these differences in the distribution of the SOD A alleles can be attributed to selectively acting processes. They explained these differences by genetic drift and stated furthermore, "that the source of the *SOD A*2* allele may be the Finnish population", from where it penetrated by gene flow into other populations. DeCroo et al. (1988) commented on the distribution of the *SOD A*2* allele as follows: "Several hypotheses have been proposed regarding the origin and distribution of the *SOD A*2* allele in different populations. However, the most likely explanation appears to be that offered by Kirk (1974), who suggested that the *SOD A*2* allele was spread across Europe by Vikings through their successive migrationsfrom their homeland in Scandinavia. The sporadic occurence of the *SOD A*2* allele in other geographically isolated groups may represent remnants of Viking penetration by themselves or by their descendants" (p. 5). This suggestion, however, cannot explain the occurence of the *SOD A*2* allele in Asiatic and African populations. It seems to be more likely, that the *SOD A*2* allele observed in these populations came into existence by independent mutations.

In India many populations from nearly all regions of the country have been typed for the SOD system. The corresponding data have been compiled by Roychoudhury and Nei 1988) and Bhasin et al. (1992). With the exception of one small group (Vania Soni, Surat, Gujarat, n=82), in which one variant has been observed, all the others showed the phenotype SOD A1-phenotype, so that one can say, that the *SOD A*1* allele is also typical for the populations of India, irrespective of their ethnic or regional origin (Bhasin and Walter 2001).

3.13. Phosphoglycerate Kinase (PGK) System (E.C. 2.7.2.3)

Chen et al. (1971) were the first, who described the existence of genetic variants of the phosphoglycerate kinase. This enzyme controls the phosphate transfer from 3-phospho-D-glycerate + ATP into 1,3-diphosphoglycerate + ADP. A defect of this enzyme results in haemolytic anaemia. Up to now five autosomal co-dominant alleles could be observed: *PGK*1 - PGK*5*. In addition to this a very rare *PGK*0* allele is known. Homozygosity of this allele causes the above mentioned enzyme defect. The gene locus lies on chromosome Xq13.3.

Concerning the PGK system only very few population studies have been reported so far. According to these studies one can suppose, that in Europeans, Asians, Amerindians, Inuits, Africans, and Australian Aborigines this red cell enzyme system is monomorphic, as only the *PGK*1* allele could be observed in them. It is interesting that according to the investigations of Blake et al. (1973, 1983) in Papuans and Oceanians the PGK system is obviously polymorphic. Thus in a sample (n=293) from the Solomon Islands the frequency of the *PGK*2* allele was observed to be 0.099. Similar high frequencies of this allele were also found in a sample from the Carolines (Micronesia), where in males (n=269) the *PGK*2* frequency comes to 0.082, in females (n=111) to 0.081. In the population of the Ulthi Atoll in the northern parts of Micronesia the *PGK*2* frequency was observed to be 0.078 (n=385), and in a Maori sample (n=77) the frequency of this allele amounts to 0.036. The *PGK*4* allele was observed in several populations of the highlands of New Guinea, where in one of the Western Highland populations the frequency of this allele comes to 0.051 (n=214). It seems that these PGK alleles came into existence in the populations of the western Pacific region and those of New Guinea, respectively, and could spread more or less by gene-flow. More population studies are needed, however, in order to understand the distribution pattern of this red cell enzyme system in detail.

In India about 30 populations from various regions of the country have been typed for this enzyme system. The coresponding data have been compiled by Roychoudhury and Nei (1988), and Bhasin et al. (1992). In all of these populations only the phenotypePGK 1 was observed, so that the *PGK*1* allele frequency comes to 1.000, which corresponds to the observations obtained on other populations (Bhasin and Walter 2001).

3.14. Carbonic Anhydrase (CA) System (E.C. 4.2.1.1*)*

The carbonic anhydrases catalyze in the erythrocytes the rapid hydration of the meta-

bolically produced CO2 from the tissues and in the loungs the dehydration of HCO3-. Three types of carbonic anhydrases are known, and for all of them genetic variants could be demonstrated, for CA I by Tashian et al. (1963), for CA II by Moore et al. (1971), and for CA III by Hewett-Emmett et al. (1983). The gene loci lie on chromosome 8q13-q22. Concerning the CA III variants so far no detailed population studies have been published, whereas the distribution of the CA I and CA II variants is fairly well known. The frequencies of all these variants are, however, rather low. However, though the frequencies of the genetic CA I and CA II variants are relatively low, some remarkable geographical distribution patterns could be observed. Concerning the CA III variants no detailed population studies have been performed so far.

CA I variants seem to be absent in Europeans, Amerindians, Inuits, Africans and Papuans, so that in these population groups the frequency of the *CA I*1* allele comes to 1.000. Against it a number of CA I variants could be observed among the populations in the Asian-Pacific area. Blake (1978) reported on the following frequencies of the *CA I*3* allele: Malayans 0.0023 (n=223), Indonesians 0.0028 (n=357), Filipinos 0.0084 (n=120), Micronesians (Guam) 0.0054 (n=468) and Micronesians (Mariana Islands 0.0041 (n=490). In two samples from Japan (Hiroshima) a *CA I*7* allele could be observed: 0.0006 (n=5511). A *CA I*8* allele was found among Parsees from Bombay (0.0212; n=307), and finally, among the Australian Aborigines the Alleles *CA I*9* and *CA I*10* were found (0.0267 and 0.0012, respectively, n=2960).

According to the so far published population studies CA II variants seem to be absent in Europeans as well as in Inuits and Amerindians with the exception of two population groups living in Brazilia: the Baniwa and the Wapishana. In the Baniwa a so-called *CA II*BAN* allele was observed (0.053, n=377), whereas in the Wapishana a *CA II*2* allele (0.002, n=614) could be demonstrated. This allele seems to be rather frequent in African populations, too, in which the average *CA II*2* allele frequency amounts to 0.079 (n=1901); the frequencies vary between 0.000 and 0.123. A *CA II*3* allele was observed among Parsees from Bombay (0.013, n=307) and among Marathi from Bombay (0.002, n=470). A *CA II*4* allele was observed among the Australian Aborigines (0.016, n=2960), but also among the Daga from the Bay Province in New Guinea (0.018, n=139). Jenkins et al. (1983) commented on this remarkable observation: "Though it was unexpected that we should find subjects phenotypically CA II 4-1 among the Daga, it was hardly surprising. It provides yet more evidence for contact between Papuans and the inhabitants of Australia, probably before the coming of Europeans" (p. 362). Apart from that in all the other Asian and Oceanian populations only the *CA II*1* allele seems to exist (Blake 1978).

The data available for India have been compiled by Roychoudhury and Nei (1988) and Bhasin et al. (1992). In most of the hitherto tested 40 populations no CA variants were seen. The fewexceptions have been mentioned already above (Bhasin and Walter 2001).

3.15. Lactatdehydrogenase (LDH) System (E.C. 1.1.1.27)

This enzyme exists in three different types: LDH A, LDH B and LDH C. It is present in all tissues and catalyzes the transformation of pyruvate into lactate. The gene loci lie on the chromosomes 11p15-p14, 12p12.2-p12.1 and 11p15.5-p14.3, respectively. Genetic variants are known for the LDH A and LDH B types, e.g. Memphis 1 and Memphis 2, Calcutta 1 and Calcutta 2 (LDH A), Delhi 1 and Madras 1 (LDH B).

Genetic variants of LDH A and LDH B could be shown in all human population groups. Their frequencies are, however, extremely low. The most interesting results were found concerning the LDH B types, which according to Mukherjee and Reddy (1983) seem to be widespread especially in India. The most frequent variant is *LDH A Cal-1* (Cal = Calcutta, where this variant was observed for the first time). The regional and ethnic variations of the frequencies of this variant are considerable. The average frequencies comes to 0.72% in South India (n=5027), to 1.54% in East India (n=2398), to 1.30% in West India (n=2535) and to 1.02% in Northern India (n=2645). Outside India this LDH variant could be observed only sporadically, e.g. on Sri Lanka, in Indonesia (Bali), on the Philippines (Manila) and on the Caroline and Marshall Islands in the Pacific region. Mukherjee and Reddy (1983) gave the following explanation for this distribution pattern: "From this sporadic occurence of Cal-1 variant outside India it may be assumed that this typical faster A subunit variant in these places has not appeared due to independent mutation, rather, it may be

due to the result of miscegenation with the outsider, possibly, with the Indian sailors, as all these places are located in the coastal area" (p. 4). And concerning origin and distribution of this variant, which on the whole is restricted to India, Mukherjee and Reddy (1983) concluded: "It can be suggested that since incidence of Cal-1 variant is highest among the Indian populations and exists in polymorphic nature, the mutant allele is of Indian origin. As there is not much difference amongst the different ethnic goups of India in respect to Cal-1 distribution and is distributed in all the regions of India, it can be strongly suggested that the Cal-1 gene is present in the Indian populations over a long time. Migration and admixture throughout the ages might have also played important role in spreading this mutant gene in various ethnic groups of Indian subcontinent" (p. 5).

LDH variants of different type were also observed in other regions of Asia, e.g. in Malaysia, China and Japan as well as in Amerindians, Africans and Europeans. The frequencies of all these variants are, however, very low. With the exception of *LDH A Cal-1* they are therefore of only little population genetical interest (Bhasin and Walter 2001).

4. HAEMOGLOBIN

Haemoglobin (HB) is a tetramer that consists of two α-like and two β-like globin subunits. These subunits are encoded by two clusters of genes each of which is expressed sequentially during development. The earliest embryonic haemoglobin tetramer, Gower 1, consists of ε (β-like) and ζ (β-like) polypeptide chains. Beginning at approximately eight weeks of gestation the embryonic chains are gradually replaced by the adult α-globlin chain and two different foetal β-like chains, designated $^{G}\gamma$ and $^{A}\gamma$. During the transition period between embryonic and foetal development, HB Gower 2 ($\alpha_2 \varepsilon_2$) and HB Portland ($\zeta_2 \gamma_2$) are detected. HB F($\alpha_2\gamma_2$) eventually becomes the predominant HB tetramer throughout the remainder foetal life. Beginning just prior to birth, the γ-globin chains are gradually replaced by the adult β-and δ-globin polypeptides. At six months after birth 97-98 per cent of the haemoglobin is $A_1(\alpha_2\beta_2)$, while $A_2(\alpha_2\delta_2)$, accounts for approximately 2 per cent. Small amounts of HB F (1 per cent) are also found in adult peripheral blood (Deisseroth et al. 1978; Embury et al. 1980; Maniatis et al. 1980). The loci for HB are assigned to chromosome 16 (16p13.3) for haemoglobin alpha and for haemoglobin beta, haemoglobin delta and haemoglobin gamma to chromosome 11 (11p.15.5).

4.1. Haemoglobin (HB) Variants

Normal adult human haemoglobin is composed of two different portions which can be separated by electrophoresis techniques; the major portion is called haemoglobin A_1 and the minor portion haemoglobin A_2. The difference between haemoglobin A and a number of aberrant human haemoglobins is a single amino acid substitution in the α or β or γ or δ chain. Most of the mutant haemoglobins have been demonstrated to be under simple genetic control. A number of haemoglobin variant are associated with or produce clinical signs. Over 470 abnormal forms of haemoglobin have been described in the literature. Of them, one third are on the alpha (α) chain, the remaining being mostly on the beta (β) chain and a few on the gamma (γ) and delta (δ) chains. The term 'haemoglobinopathies' covers the group of hereditary abnormalities in which either the structure (e.g. HB S, HB C, HB D, HB E) or the rate of synthesis (thalassaemias) of normal haemoglobin is altered.

A close concordance between the geographic distribution of endemic malaria and that of high frequency haemoglobin variants, thalassaemias and other red cell defects have been observed which represents one of the principal factors leading to the general acceptance of the malaria hypothesis i.e., in a malarial environment, selective forces have acted to preserve heterozygotes of haemoglobin variants because of their advantage against malarial infection (Allison 1954 a,b, 1964; Livingstone 1957, 1967, 1971, 1983; Rucknagel and Neel 1961; Motulsky 1964; Durham 1983). The selective resistance of the heterozygote illustrates the concept of balanced polymorphism and may be contributory to the maintenance of high allele frequency in a particular area. It is possible that there are still other factors that maintain this genetic equili-brium.

The general incidence of haemoglobin variants has been observed about 0.5 per cent from the Indian region. The abnormal haemoglobins observed among various population groups are HBS, HB E and HB D. The relatively rare abnormal haemoglobins reported from this

region are HB J, HB K, HB L, HB M, HB Q, HB Lepore, HB Norfolk and the hereditary persistence of HB F. There are two principal types of thalassaemia namely alpha and beta. Beta thalassaemia is of two types: (i) Beta-thalassaemia major on which studies are available from all over India and (ii) Beta-thalassaemia minor, which is mostly reported from north and east India. Alpha thalassaemia is present in two forms: (i) Haemoglobin Barts and (ii) Haemoglobin H.

1. Haemoglobin S (HBS)

One of the most interesting human haemoglobin mutant has been designated S, $Hb\alpha_2^A\beta_2^S$. The notation signifies that the mutation has affected the β-chain. In homozygous individuals $Hb\alpha_2^A\beta_2^S$ and small amount of $Hb\alpha_2^A\delta_2^{A_2}$ are found. In heterozygous individuals three components are found $Hb\alpha_2^A\beta_2^A$, $Hb\alpha_2^A\beta_2^S$ and $Hb\alpha_2^A\ \delta_2^{A_2}$. Haemoglobin S may be separated from haemoglobin A by electrophoresis or by performing sickling test on fresh blood. The sickling of red cells of homozygotes (Hb SS-*HB*S/HB*S*) is more severe than that of heterozygotes (HB AS-*HB*A/HB*S*).

Genetic load of sickle cell anemia is indeed very high affecting not only the health and physical performance but poses also a challenge to the health services. It is estimated that 186096 cases of sickle cell anaemia are present in the Indian sub-continent. Each patient is not only burden on the health services but also affects normal family life (Bhatia, 1987).

The sickle cell trait occurs with highest frequency in tropical Africa (0.100 to 0.400), with high frequency in India, Greece and Southern Turkey (0.050 to 0.100) and less than 0.100 among the population groups living around the Mediterranean Sea (Palestine, Tunisia, Algeria and Sicily) and shows a distribution continuous throughout these areas.

Among the problems which the abnormal haemoglobins present is the one of interaction of alleles for the β-chain variants. Haemoglobin S is also known to occur with other abnormal haemoglobins. They are: Sickle cell HB C (*HB*S/HB*C*), Sickle cell HB D (*HB*S/HB*D*), Sickle cell HB E (*HB*S/HB*E*), Sickle cell Thalassaemia (*HB*S/β*THAL*), Sickle cell associated with foetal haemoglobin other than during infancy.

With regard to the origin of sickle cell gene, there has been much debate whether the extensive geographical occurrence of sickle-cell disease can be explained by a single origin of the mutation with subsequent large scale migration in prehistoric times or whether it relates to multicentric origins (Lehmann 1953; 1954a,b, 1956-57; Lehmann and Cutbush,1952 a,b; Lehmann et al. 1956; Livingstone 1967). These queries have been examined by an analysis of restriction site polymorphisms (RFLPs) linked to *HB*S* globin gene; Kan and Dozy (1980) observed differences in the association of sickle cell gene which constituted a base for the hypothesis of multiple mutation origin of *HB*S*. Subsequently studies of an array of RFLPs linked to the *HB*S* mutation in Jamaicans (Wainscoat et al., 1983; Antonarakis et al. 1984), U.S. Americans (Antonarakis et al. 1984) and African Blacks (Pagnier et al. 1984) strongly supported the hypothesis that the *HB*S* mutation has arisen independently on several occasions in Africa. The distribution of the different *HB*S* haplotypes among six different population groups of Africa and Asia by Kalozik et al. (1986) provided strong evidence for an independent Asian origin of mutation. Migration of West African population carrying *HB*S* Mutation to North Africa, the Mediterranean and West Saudi Arabia is suggest-ed from the analysis but no haplotype has been found by them in their Indian and East Saudi Arabian samples that predominantly showed the major Asian *HB*S* mutation. They further added that whether the Asian *HB*S* mutation originated in East Saudi Arabia and spread to India possibly with the Arab expansion in the first millennium A.D. (Bowles 1977) as suggested previously (Lehmann et al. 1963) or vice versa, possibly carried by Indian Arabic trade routes (Bowles, 1977) is not known. They concluded that the geographical distribution of Asian *HB*S* haplotype as observed by them corresponds to the reported distribution of mild homozygous SS (*HB*S/HB*S*) disease associated with high levels of HB F (Ali, 1970; Haghsenass et al. 1977; Pembrey et al. 1978; Perrine et al. 1978; Brittenham et al. 1979; Weatherall and Clegg 1981; Acquaye et al. 1985; Bakioglu et al. 1985).

The HB S trait is prevalent in Africa with lesser frequencies in the Mediterranean basin, Saudi Arabia and also in India where average *HB*S* frequency is 0.031. Geographic and climatic factors have been suggested as determinants for the understanding of the observed variations (Charmot and Lefevre-Witier 1978; Lefevre-Witier

1985). The frequency of *HB*S* is highest in the peninsular plateau (0.039), whereas in other natural regions, the allele is either absent or present in a very low frequency. The frequency of *HB*S* is quite high in semiarid steppe type region (0.071) followed by tropical savannah type region (0.039) as compared to monsoon type with dry winter region (0.003) (Bhasin et al. 1994).

It was in the Nilgiri Hills that sickle cell trait was first detected in India (Lehmann and Cutbush, 1952a,b,c) and among Indian populations the frequency of this trait is 0.031 (varies from complete absence to 0.410). It is present in high frequency among the scheduled tribes (0.054) as compared to other ethnic groups-caste (negligible), scheduled caste (0.024) and community (0.011). The trait is reported to be present among scheduled castes and communities, who are living in close proximity with tribal populations. Therefore apparently the trait has been transmitted among these groups due to admixture with tribal groups (Bhasin and Walter 2001).

2. Haemoglobin E (HBE)

Unlike haemoglobin S, both the homozygote and heterozygote of haemoglobin E (β chain variant) are found in healthy individuals. Similarly, those individuals which have a combination of sickle cell and HB E (*HB*S/HB*E*) also seem to be healthy.

The HBE, first reported in a child whose father was partly of Indian origin, has since then been found in Thailand, Burma, North Eastern Malaya, Indonesia, Assam, Bengal, Nepal, Ceylon and in an Eti-Turk.

The β^E-globin gene is quite common in Southeast Asia (gene frequencies approaching as high as 0.20 to 0.30) and presumably it produces mild form of β-thalassaemia (Orkin et al. 1982) and thereby is under a positive selection in areas in which malaria is endemic. Using restriction analysis multiple origins of β^E mutation have been pointed out. In fact, β^E mutation has been observed in five different haplotypes (restriction endonucleases), three in Southeast Asians (Antonarakis et al. 1982) and two in Europeans (Kazaziani et al. 1984). These haploytpes may be found in association with two different β-globin gene frameworks in Southeast Asians, and a third framework in Europeans. Using restriction analysis at eight restriction sites, Hundrieser et al. (1988a) studied Bodo group - Kachari of Tibeto-Burman languages in Assam among whom highest known prevalence of haemoglobin E has been reported (Das et al. 1988) and found a common origin of the *HB*E* gene in Southeast Asia and Assam. This was surprising since main area of the distribution of *HB*E* is Southeast Asia and in contrast other Assamese populations e.g. Ahom and Khasi, the Tibeto-Burman groups have no direct links with Southeast Asians.

The pattern of distribution of *HB*E* and malarial infection in Southeast Asia and North East India suggest the introduction of *HB*E* from Southeast Asia and attainment of higher frequencies in certain populations, probably because of continued selective pressure of malarial infection (Saha 1990).

Haemoglobin E, one of the most frequent haemoglobin variants, occurs principally in populations of Southeast Asia. Within this region *HB*E* has been found with a frequency of nearly 0.60 in some isolated areas (Flatz 1967; Na-Nakorn et al. 1956; Na-Nakorn and Wasi 1978; Wasi et al. 1967; Wasi 1983); the highest incidence occurs at the junction of Laos, Thailand and Cambodia in what has been referred to the the *"HB*E Triangle"* (Na-Nakron and Wasi 1978). Among Filipinos *HB*E* is almost absent. In general, all over Indonesia the frequency of *HB*E* varies from 0.01 to 0.05 and in Malayan population it ranges inbetween 0.05 and 0.10 with a few exceptions. Among Burmese the overall incidence is around 0.25 to 0.30. From East Asia, the *HB*E* frequency is reported 0.01 to 0.02. It is absent among Tibetans. Among the populations of Southwest Asian region the *HB*E* has not been observed, except among Iranian, where it is reported about 0.01. From Indian region, the frequency of *HB*E* is reported from 0.004 to 0.040 among Nepalies. Its frequency is around 0.01 to 0.05 from Bhutan. The *HB*E* frequency is less than 0.01 in the populations from Pakistan and it is also observed among Bengali Muslims of Bangladesh. *HB*E* is present in Bengal and in high frequency in Assam; in other parts of India sporadic cases have been reported. Livingstone (1964) stated that there appears to be a stronger neighbourhood of Calcutta with *HB*E* predominating in the east and *HB*S* in the west. *HB*E* was suggested as a marker for the Mongoloid element in Northeast Indian populations (Flatz 1978).

A low frequency of *HB*E* has been observed among Sinhalese, Tamils and Muslims of Sri Lanka by Saha (1988a). Whereas Veddahs in Sri

Lanka have been reported to have a high frequency of *HB*E* (Kirk et al. 1962b; Wickremasinghe et al. 1963), Wickremasinghe and Ponnuswamy (1963) found no *HB*E* in more than 1000 samples of Sinhalese, while De Silva et al. (1959) had reported a high frequency in one locality of Sri Lanka apparently due to admixture with Veddahs in that area. An important feature to note is that the incidence of *HB*E* is very low and is present in both the Sinhalese and the Tamils of Sri Lanka. Saha stated that this suggests that *HB*E* has originated within the Veddahs rather than being introduced from Southeast Asia, in which case the incidence should have bene greater in the Sinhalese, contrary to Kirk's (1976a) suggestion. *HB*E* has also occasionally been reported among Europeans (Fairbanks et al. 1979).

In Thailand a reduced fertility of HB E homozygotes (*HB*E/HB*E*) compared to that of heterozygotes has been demonstrated (Flatz et al. 1965; Höftlinger 1971). But no differential fertility or mortality in respect of *HB*E* genotypes among the Kacharis of Upper Assam is observed by Deka (1976). The adaptive advantage of *HB*E* alleles in areas of endemic malaria in Thailand (Flatz 1967; Kruatrachue et al. 1969) are not detected in Assam (Deka 1976), in spite of wide prevalence of falciparum malaria. Das et al. (1980) observed that these findings appear to corroborate their earlier suggestion (Das et al. 1975; Deka 1976) that the *HB*E* polymorphism in Bodo populations of lower Assam is of transient nature as *HB*E* allele tends to replace both HB T and HB A.

The frequency of *HB*E* in Indian populations varies from complete absence to as high as 0.646 among Boro Kachari of Assam with average frequency of 0.023. Among caste groups the frequency is low (0.002) as compared to other groups-scheduled caste (0.009), scheduled tribe (0.029) and community (0.030). The highest frequency *HB*E* is observed from Indus-Ganga-Brahmaputra plains region (0.114) as compared to other regions.

Among Indian populations the incidence of haemoglobin variants is about 0.005. *HB*S* allele with a frequency ranging from complete absence to 0.410 is present among them with a general frequency of 0.031. It is prevalent among the scheduled tribe followed by scheduled caste groups but is almost absent in the caste groups. Its frequency is high in semi arid steppe type of climatic region (0.071) as compared to others. It is present in high frequency in Central India followed by South, West and North India. The frequency is quite low in East India and the allele is absent in Islands zone. *HB*S* frequency is high in Dravidian language family (0.047) but it is lacking in Tibeto-Chinese language family. With regard to the origin of sickle cell gene, Kan and Dozy (1980) proposed the view that Indian and West African sickle cell gene mutations arose by separate events. The *HB*E* is observed in high frequency among the population groups of East India particularly from Eastern Himalayan region where the frequency is 0.237. The frequency of *HB*E* is high in speakers of Mon Khmer group of Austro-Asiatic language family, as well as among the speakers of Tibeto-Chinese language family from Eastern Himalayan region. Heterogeneity of the *HB*E* allele has been recently observed both in Southeast Asia and North-east India. A selective advantage of *HB*S* and *HB*E* against malaria could not be corroborated in the Indian populations. The low frequency of *HB*E* at high altitude is suggested to be due to relaxation of selection (Bhasin 2009; Bhasin et al. 1994; Bhasin and Walter 2001).

4. DNA POLYMORPHISMS

Recently, with the unique combination of new discovery (new enzymes, nucleic acid hybridization and the Polymerase Chain Reaction), today the DNA (deoxyribonucleic acid) has become the easiest macromolecule of the cell to study. This development of technology in the field of DNA analyses has opened new channels in the study of human population genetic diversity and relationships. DNA can be easily purified from any nucleated cell of the body and once isolated it is much more stable than many other macromolecules. It can be cut very precisely and reproducibly with restriction enzymes, enabling excision of specific piece of DNA, which can be cloned in unlimited quantities, similarly a target DNA can also be amplified in numerous copies by PCR. Hybridization technique and rapid sequencing method for the amplified DNA have enabled us to study the genes themselves directly, unlike their indirect investigations through their immunological (i.e. blood groups) and biochemical (i.e. protein and enzyme polymorphisms) products. Preliminary results from nuclear and mitochondrial restriction fragment length polymorphisms (RFLPs) have led molecular geneticists to put forward new hypo-

theses about human type phylogenies Recently there is an explosion of studies using several DNA markers (like single nucleotide polymorphism, SNPs; restriction fragment length polymorphism, RFLP; minisatellite or variable number of tandem repeats, VNTRs; microsatellite or short tandem repeats, STRs; mitochondrial and Y chromosome markers) to study the genetic variability and phylogenetic relationships of human populations (Cann 2001; Basu et al. 2003; Cavalli-Sforza and Feldmann 2003; Kivisild et al. 2003; Cordaux et al. 2004; Jorde and Wooding 2004). Now many phylogenetic trees on world wide human populations are put forth using the mtDNA and Y chromosomal DNA markers to understand the evolution of modern human (Wallace 1995; Hammer et al. 1997, 1998; Hammer and Zegura 2002; Underhill et al. 2000, 2001; Underhill 2003; Bamshad et al. 2004; Cavalli-Sforza 2005; Hunley and Long 2005 among others). Reddy (2008) has edited a special issue on Trends in Molecular Anthropology in which genomic diversity mainly in and among different populations of India has been reported.

The use of polymorphic DNA segments as markers for inherited diseases has greatly expanded the potential utility of the classical methods of linkage analysis and has already contributed considerably to our knowledge of human genome pathology (Reich et al. 2001; Collins et al. 2003; Wall and Pritchard 2003; McVean et al. 2004; Tishkoff and Kidd 2004)

Biological anthropology has achieved new strides after Washburn's 1951 statement. For grasping the laws and processes of human evolution, molecular evidences have been marshalled, leading to the advent of microscopic work in the area. Human cytogenetics has made an outstanding contribution towards the knowledge of adaptation and evolution. Evolution at the genic (elemental) level is that which is being sought through DNA analysis using recombinant techniques. Thus, we have come a long way from morphological studies (morphological, behavioural, anthropometric, and dermatoglyphic traits - the mode of inheritance of all these characters is still rather unclear) to those of genetic or classical markers (blood groups and protein markers), and to the newly discovered molecular techniques which have provided a new direction and a whole battery of powerful polymorphic systems to study genetic diversity. The question, what happens to genes with degradation in biotic environment, acquires a primary place. With these newer and still newer interests, different kinds of techniques have been enunciated to understand nature-nurture relationship in a better fashion. Moreover, there has been a concomitant advancement in statistical methods and we are now in a position to make use of many parameters.

In India, the differences in various biological traits due to diversity of ethnic composition of the Indian population, consisting as it does of elements of autochthonous, Caucasoid and Mongoloid origin, are well documented. The Indian populations have interbred among themselves in varying degrees to give mixtures which are difficult to unravel. Some of the processes of change–mutation, genetic drift and linkage equilibrium are almost totally uninfluenced by environment but one of these processes–natural selection–is so dependent. To some extent, the pattern of frequencies distribution of various biological traits is to be regarded as the result of natural selection related to the harmful effects of particular climatic and other local features of the environment. However, one still cannot know at all precisely which environmental features are involved, but these almost certainly express themselves by tending to cause particular diseases, to which people of certain genetic marker group are more susceptible than anothers.

In addition to mutation, genetic drift and natural selection, severe epidemics, floods and famine have at various times over the centuries reduced the populations of different zones, and of India as a whole, to levels where great accidental fluctuations of gene frequencies were possible. Such fluctuations seem indeed to have occurred, as the frequencies observed at present bear less relationship to those of the original migrants and/or invaders.

It is needless to say that there is still a need for assimilation of the new results, and for further studies on similar lines. There are still important gaps in our knowledge of the frequencies of genetic markers of key populations (for details *see* Bhasin et al. 1992). Gap-filling tests on selected populations would make it possible to use the existing observations much more efficiently in working out the population structure. The regional and ethnic distribution of the numerous nuclear and mitochondrial DNA polymorphisms, which turned out to be of highest importance to population genetics. This could be shown e.g. recently by various investigators who studied

the genomic diversity in and among different populations of various parts of the world (Bhasin and Walter 2001)

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