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Glycophorin-A Allelic Distribution Frequency in South Indian Population

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ABSTRACT Lansteiner and Levine described a blood group system in 1927 called the MN system. According to this theory, three possible genotypes MM, MN and NN occur. The antigenic determinant of human MN system on erythrocytes is a sialogylcoprotein with a chain of 151 amino acids. It is regarded that about 50% of the population will express the MN heterozygous genotype as this is based on the Mendalian inheritance. Studies on the distribution frequencies of blood groups and subgroups of a population is one way to understand the population's genetic makeup and susceptibility to disease. Blood samples were collected from 413 south Indian volunteers who were chosen randomly for the blood grouping of MM, NN or MN types. The data was recorded and the gene frequencies for the MN, NN and MM types were calculated using the standard statistical analysis. The results show that approximately 50% of the population is heterozygous for MN and fits into Hardy-Weinberg equilibrium.

INTRODUCTION

Lansteiner and Levine described a blood group system in 1927 called the MN in which two alleles M and N determine the presence of corresponding antigens on red cells. According to this theory, three possible genotypes MM, MN and NN occur. GPA genes code for the determinant molecule for the MN blood group in erythrocytes and are present on the 4q29 chromosome site. The GPA of human erythrocyte is a sialogylcoprotein with a chain of 151 amino acids and a molecular weight of 55,000 Daltons. The M and N forms vary in their amino acid composition in positions (1) and (5) (Furthmeyer, 1978). The M group has Serine and Glycine in positions (1) and (5) respectively and the N group has Leucine and Glutamic acid in the respective positions. It was shown unambiguously that GPA either can be totally absent from human erythrocytes or that the protein can be altered so extensively that it can no longer be recognized (Furthmeyer, 1978). This might be because of the mutations at the locus, which was unexplained at that time. The aminoacid sequence of the GPA is different in positions 1 and 5, but no differences in carbohydrate structure or sites of glycosylation (*) are apparent for the two forms.

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A^N Leu-Ser*-Thr*-Thr*-Glu
A^M Ser-Ser*-Thr*-Thr*-Gly

It was also suggested that (Furthmeyer, 1978) that the two forms of the GPA evolved from a common ancestral gene by single base substitutions at the sites in the genome coding for aminoacids in positions 1 and 5 of the sequence.

The human GlycophorinA is a sialogylcoprotein of 151 amino acid and spans the erythrocyte membrane in about 5 x 10^5 copies per cell. The protein is present as two forms and three possible genotypes MM, NN or heterozygous MN can occur in a given population. It is regarded that about 50% of the population will express the MN heterozygous genotype as this is based on the Mendalian inheritance. The MN blood group system is under the control of an autosomal locus found on chromosome 4, with two alleles designated L^M and L^N. The blood type is due to a glycoprotein present on the surface of red blood cells, which behaves as a native antigen. Phenotypic expression at this locus is co-dominant because an individual may exhibit either one or both antigenic substances. Frequencies of the two alleles vary widely among human populations. The M and N determinants on the red cells are inherited by means of two allelomorphic genes M and N at a single locus (independent of ABO and of P1P2) but there is no dominance or recessiveness, so that while the cells of MM homozygotes are agglutinated by anti-M and those of NN homozygotes by anti-N, those Of MN heterozygotes are agglutinated by both antisera.

Studies on the distribution frequencies of blood groups and subgroups of a population is one way to understand the population's genetic makeup and susceptibility to disease apart from a host of other applications. Monospecific antibodies are required against the two GPA variant forms primarily to differentiate the three possible phenotypes (MM, NN and MN).

MATERIALS AND METHODS

Blood samples were collected from 413 South Indian volunteers who were chosen randomly for the blood grouping of MM, NN or MN types. Blood typing was done using commercial antisera for M and N types from Ortho Clinical Diagnostics, USA using standard agglutination methods on glass slides. The data was recorded and the gene frequencies for the MN, NN and MM types were calculated using the standard statistical analysis.

RESULTS

The results obtained from the population study with respect to the frequency of MM, MN and NN blood groups are given in

Table 1: Phenotypes and genes frequencies of MN blood groups in the South Indian population

Blood group	*Number observed*	*Number expected*	*Genes frequency*
M	121	117.73	$M = 0.5339$
MN	199	205.55	
N	93	89.72	$N = 0.4662$
Total	413		

$\chi^2 = 0.4194$

The differences between the expected and the observed frequencies of these blood groups are not significant. The genotype frequency for MM blood group was 0.2929 (p^2) and for MN blood type was 0.4818 (2pq). The same for NN blood type was 0.2251 (q^2). The allelic frequency for M and N types was 0.5338 and 0.4662 respectively. The expected genotype frequencies for MM, MN and NN types were 0.7071, 0.5182 and 0.7749 respectively. The results show that approximately 50% of the population is heterozygous for MN and fits into Hardy-Weinberg equilibrium.

DISCUSSION

Studies on a section of our population indicate that the distribution of the blood groups fits into Hardy-Weinberg equilibrium, as the genotype frequencies are constant. This reiterates that nearly 50% of the population falls within the heterozygous MN category.

Because anti-M and anti-N occur only extremely rarely in human serum there is almost no danger of their causing trouble in blood transfusion. Thus they have been recognized as of little importance in medicine, and testing has largely been left to geneticists. Thus data on the distribution of the M and N groups has built up only very gradually over the years. The genetics of the system seem to imply that the N antigen is actually a precursor substance and the N gene is an amorph which leaves the N antigen unchanged while the M gene of the heterozygote converts part of the N antigen into M, and in the homozygote converts nearly all of the precursor to M. The MN antigens seem to have a direct interaction with membrane bound sialic acids, as M and N specificities seem to be linked to the presence of sialic acid variations. It has been suggested that the antigenic variations may result from specific sialyl transferase activities, which transfer sialic acids to disaccharides bearing specific T and Tn specificities that characterize specific cryptic antigens.

When the MN system was first discovered it appeared rather uninteresting. It was of virtually no medical importance, and the frequencies of the M and N genes were closely similar, each near 50 per cent, in most populations available for testing. Only the American Indians, with much more M than N, relieved this uniformity. Around 28% of the population type out as MM, 22% as NN and 50% as MM. The discovery of the S and s antigens in 1947 and 1951 came at a fortunate time, for a model of closely linked genes in the Rh system had been very thoroughly studied, and so it was soon realized that here again closely linked loci were involved, two in number, one determining the alleles M and N and the other S and s. Thus in the MN system we now have the possibility of four haplotypes MS, Ms, NS, and Ns and this expansion of the system greatly enhances its anthropological value.

Of late, several associations with health conditions have surfaced with respect to the MN phenotypic expression in people. Most health problems are associated with the two "purebred" types (NN and MM), not with the mixed type (MN), a phenomenon known in genetics as hybrid

vigor. It appears that the MN system may play a role in breast cancer. In general, persons with a family history of cancer are both Type A and MM, it is probably advisable that he or she adopt an aggressive cancer prevention lifestyle.

There is also a potential role for the MN system in cardiovascular disease. A 1983 study in the Journal Clinical Genetics showed that people who typed NN had significantly higher cholesterol and triglyceride levels in their blood immediately after being given a standard test meal. The researchers concluded that people who have at least one M gene (blood types MM and MN) seem to be better protected against rapid rises in their triglycerides and cholesterol. Possible association with the MN phenotypic expression to human health concerns comes from a number of studies. These include MN locus haplotypes with essential hypertension (Heise, 1987; Miller, 1979), Spinal osteochondrosis (Kolodchenko, 1979), and also the effects of the MN blood group expression to serum LDL cholesterol level to a low fat diet (Birley, 1997)

An interesting application of the knowledge of the phenotypic expression of the MN system in humans comes from the usefulness of the Glycophorin-A mutation assay, which is primarily a biodosimetric technique and is a reasonably good indicator of human health risk assessments. Mutational assays at the GlycophorinA locus developed till date use both the forms of monoclonal antibodies to detect the loss of the gene products from either of the two allelic forms (Langlosis, 1986). Monoclonal antibodies facilitate the detection of mutant erythrocytes lacking either the N or the M products of the alleles among normal erythrocytes from the MN heterozygous individuals. The variant cell types, which can be detected, are those that lack the M form of the protein and those that lack the N form of the protein (Akiyama, 1995). The erythrocytes are fixed and stained using monoclonal antibody-fluorochrome conjugates (Langlosis, 1986). The erythrocytes are therefore doubly stained and the enumeration of the variant cells can be done by flow-cytometric analysis (Jensen, 1995). Although polyclonal typing sera are commercially available, monoclonal antibodies for the two forms of the human GPA became a necessity for the GPA mutation assay as initially developed, which employs Flowcytometric studies.

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