SEROLOGICAL AND BIOCHEMICAL GENETIC MARKERS AND THEIR ASSOCIATIONS WITH PSYCHIATRIC DISORDERS: A REVIEW

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SUMMARY

The studies pertaining to associations of serological and biochemical genetic markers (blood groups in particular and serum proteins and enzymes in general) with the psychiatric disorders such as psychoses in general, schizophrenia, manic-depressive psychosis including unipolar and bipolar affective disorders and neurasthenes have been critically examined. The reasons for inconsistent findings of various investigators have been pointed out to assist the future researchers to overcome the previous drawbacks. Implications of associations of genetic markers with the psychiatric disorders have been discussed and future areas of research suggested.

In human beings a number of genetic polymorphisms exist which manifest variable susceptibilities towards pathogenesis and aetiology of a particular disease. As nature has generated and maintained a variety of balanced polymorphisms, it seems logical that some genetic markers might be serving some hidden important biological functions unknown to human. Natural Selection, in addition to some other factors, plays a vital role in maintaining this balanced polymorphism in populations because different genotypes have different health and survival values to individuals. A defective or abnormal genotype is deliberately deleted or eliminated through Natural Selection because of its lethality or unduly susceptibility to a disease. If for this relationship any substantial evidence is obtained then that information may be highly relevant and of tremendous help not only in unfolding the mystery shrouding the probable role of Natural Selection and its mechanism of action, but also its application as a genetic tool for differential diagnosis in clinical medicines. For understanding biological significance of polymorphisms in man, special attention is being diverted towards the relationship between the genetic markers and human diseases.

The implications of the association between serological and biochemical markers and diseases in relation to the genetic aetiology of a disease are ample in medical genetics. The fact that a serological or biochemical marker will influence disease susceptibility implies that some product related to gene determining serological or biochemical trait, or possibly the product of some closely linked gene takes part in the complex mechanisms influencing diseases, and that the mechanisms are extremely prone to influence which are not yet understood. Such diseases are also likely to manifest in different environmental factors. It would, therefore, be reasonable to postulate that blood group factors or very closely linked genes represent one among many other relevant variables which are both innate and acquired. The contribution of blood group variations to the variation in disease susceptibility is justifiable to the assertion that blood group associations imply the hereditary causation in the aetiology of a disease.

After reviewing and evaluating the dermatoglyphic associations with various psychiatric disorders (Balgir, 1982; Balgir and Srinivasa Murthy, 1982; Balgir, 1983), the ample accumulated but scattered data concerning the correlations between various serological (blood groups)
and biochemical genetic markers, and psychiatric disorders allow us to examine these associations comprehensively.

Before proceeding for the review, it becomes essential to clarify that under the category of serological and biochemical genetic markers only the blood groups in particular and, serum proteins and enzymes in general have been examined for associations, although a number of other genetic markers exist in human beings. Secondly, all the studies pertaining to drug metabolism and linkage have been deleted. Thirdly, general drawbacks in various studies have been pointed out collectively and in a summarized form at the end of each section.

The following is a review of the broadly defined nosologic categories of psychiatric disorders:

PSYCHOSES

The studies pertaining to association of serological (blood group) traits with the mentally ill were started early in the present century with the discovery of blood groups in 1900 A.D. One of the earliest studies of blood group association was that of Ghominskij and Sustova (1928) who reported that in 500 cases of endogenous psychoses, the phenotype A was markedly increased. Later a majority of the workers, however, observed no difference between normal blood group distribution and that occurring in persons suffering from mental disorders. Proeschcher and Arkush (1927) had already mentioned that the type of psychosis cannot be determined from the blood groups. Bravetta (1930) after examining 1000 mentally affected persons, expressed similar views. Penrose (1932) did not find conspicuous relationship between ABO blood group distribution and 166 cases of Mongolism. It was the same as that for other mentally deficient patients. Bianchini (1937) studied 700 mentally affected persons and compared them with the normals, to found no difference between the group. Similar were the observations of Thomas and Hewitt (1939).

Herman and Derby (1937) investigated the MN system in 1849 cases of psychosis and found a normal distribution between controls and the patient group.

In a unique study conducted by Op Den Velde and Stam (1973), an increase of haptoglobin (IF and IS) genotypes was observed in 120 patients with a clinical diagnosis of Alzheimer's disease and senile dementia. The abnormal haptoglobin sub-type distribution was most striking in patients with an early onset of dementia. Thus a lack of a positive correlation between the serological and biochemical traits and mental abnormalities may be attributed to unclearly defined diagnostic criteria, nosologic categories of the patients, their selection and also unrigorously collected controls (generally the blood donors were assumed to be healthy and representative of the normal population although the donors represent slightly excess of 0 phenotype over other individuals, 0 being the universal donor). Hence these studies were only of historical importance.

SCHIZOPHRENIA

Exhaustive studies were carried out in Schizophrenia regarding the association of blood groups during the period 1927-33. Earliest available report in the literature is that of Ghominskij and Sustova (1927) who examined 276 patients suffering from Schizophrenia and found an increase in the blood group A, while Wurz (1928) observed a somewhat decreased incidence of blood group B in subjects afflicted with Schizophrenia. However, Raphael et al. (1927) noted a normal distribution in 800 subjects suffering from Schizophrenia and 300 manic-depressives. According to Gundel and Tornquist (1929), there was
an increase of B and AB blood groups in schizophrenia. On the other hand, Espejo Sola (1931) observed a normal ABO blood group distribution in 107 cases of schizophrenia, and similar observations were made by Somogyi and Angyal (1933) in 411 cases of schizophrenia. Due to lack of compatible findings, a depression is observable between 1933-1963.

Irvine and Miyashita (1965) also tried to find association between blood groups and schizophrenia. Among 668 mental hospital admissions, blood groups A (and A1), O, E and Kell tended to associate, respectively, with schizophrenia, manic-depressive psychosis, neurotic depressive reaction, and depression in general and the results were statistically significant. Dharmarajan and Rodricks (1972) studied the blood group distribution in cases of schizophrenia, epileptic psychosis and mental defectives, but failed to find any conclusive results.

Lovegrove and Nicholls (1965) examined the association between haptoglobins and schizophrenia and came to the conclusion that the comparison of hospitalized male schizophrenics with apparently normal men revealed no evidence of significant differences in the incidence of genetically determined serum haptoglobins and these results agreed with those of Gohler and Gohler (1963). The role of haptoglobin studies in the diagnosis and investigation of schizophrenia was emphasized by Fernandez Sandonis et al. (1971). They found higher serum haptoglobin levels in schizophrenics as compared to the normal subjects. This finding was particularly obvious in the hebephrenic, catatonic forms and in patients exhibiting aggression.

The distributions of plasma group specific component (Gc) and haptoglobin (Hp) phenotypes of a large group of schizophrenic patients were compared with those of an unselected group of normal blood donors by Brackenridge and Jones (1972). It was found that about 10% fewer Gc heterozygotes and 5% fewer Hp heterozygotes existed among the schizophrenic than the control group.

Recently in a study of protein and enzyme polymorphisms in affective disorders, Parisi et al. (1980) found no association of haptoglobin and glucose-6-phosphate dehydrogenase (G-6-PD) enzyme deficiency between controls and schizophrenics. This may be due to the fact that they treated schizophrenics as a single group rather than the heterogeneous group.

The relationship of schizophrenia with the ABO and Rh blood groups and secretor/non-secretor status of the blood group specific substance was investigated by Dutta and Jetley (1973) in 200 schizophrenics. Although the ABO blood groups failed to associate with the disease, the proportion of secretors was somewhat larger among the O phenotypes as compared to others in the disease group as against the control group where the proportion of secretors was more or less similar in all the phenotypes, thereby indicating an enhanced susceptibility of O group secretors to schizophrenia as compared to the secretors of any other ABO group systems.

A survey of 46 publications on ABO blood groups among patients with depressive, schizophrenic, somatic and psychosomatic illnesses was presented by Maurer Groei (1974) where the patients were compared with matched controls. The findings of Mendlewicz et al. (1974) confirmed the majority of the findings previously reported that there is a high frequency of blood group A in schizophrenics and a high frequency of O blood group in manic-depressives. They concluded that ABO genotypes play a vital
role in the predisposition of an individual to manic-depressive illness and schizophrenia. A slightly but not significantly higher frequency of blood group A and a lower frequency of group O in schizophrenics when compared to a large group of blood group A and a lower frequency of group O in schizophrenics when compared to a large group of blood donors after proper adjustments for ethnic distributions was reported by Turgman et al. (1975). Diebold (1976) demonstrated significant differences in the distribution of ABO, Rh and MNs blood groups in schizophrenics and control population. Flemenbaum and Larson (1976) in a sample of 312 psychiatric patients tested for ABO and Rhesus blood groups found a significant increase of A blood group in manic-depressive psychosis and O blood group in schizophrenia.

The up-to-date knowledge warrants the heterogeneity of schizophrenia, being group of syndromes. The unequal representation of each sub-category may be accounted for the exaggerated findings of the above investigators regarding the association of serological and biochemical traits with schizophrenia. The hospital used by various investigators as controls may not be truly representative of the normal control population of the region. Therefore, these discrepancies may possibly be responsible for inconsistent findings.

MANIC-DEPRESSIVE PSYCHOSIS

A number of studies have been conducted on the association between affective disorders and ABO blood types, but results have been contradictory. Thomas and Hewitt (1939) studied the ABO blood groups in mentally affected persons but did not find any association. Parker et al. (1961) compared the frequencies of ABO blood groups in manic-depressive patients with a control group of neurotic depressives and reported figures for the general population. They found that the incidence of type O blood was significantly greater in the manic-depressive group than in the general population as well as the neurotic depressive group. Irvine and Miyashita (1963) compared blood group frequencies among patients with different psychiatric diagnoses and found a significant association between blood group O and involutional melancholia. Masters (1967) reported that 71% of the patients diagnosed as manic-depressive had blood group O, the frequency being higher than among schizophrenics and normal controls.

Tanna and Winokur (1968) compared the frequency of ABO blood groups in patients with primary affective disorders with their first degree relatives who had no evidence of an affective illness. They could not confirm the reported high frequency of blood group O among the primary affective group. On the other hand, the findings of Mendlewicz et al. (1974) confirmed a significantly higher frequency of blood group O in manic-depressive group and a correspondingly lower frequency of blood group A than normal controls. However, Maurer Groeli (1974) found blood group A significantly more frequent in endogenous depression and phenotype O in bipolars. Other studies failed to reveal any relation between bipolar affective disorder and ABO blood types (Bourgeois and Trejaut, 1967; Gaekwad et al. 1972; James et al. 1977).

Studies of Rh blood groups in affective disorders (Parker et al., 1961; Irvine and Miyashita, 1965; Masters, 1967; Mendlewicz et al., 1974; Beckman et al., 1978c) have mostly been negative. However, Parker et al. (1961) found an increased frequency of the E (Rh) factor in patients with psychoneurotic depressions, compared to the patients with manic-depressive psychosis.
Diebold (1976) demonstrated significant differences in the distribution of ABO, Rh and MNSs blood group systems in patients suffering from neurotic disorders, manic-depressive psychosis, schizophrenic psychosis and organic syndromes and compared to the normal population, but the results are difficult to interpret because of the unclear way of presentation of the data. Flemenbaum and Larson (1976) in a sample of 312 psychiatric patients tested for ABO and Rh blood groups, found a significant increase of A blood group in manic-depressive psychosis and O blood group in Schizophrenia.

In the MN system, Baker et al. (1977) found a decreased frequency of the N factor. Masters (1967) and Beckman et al. (1978c) found normal MN frequencies. However, the study by Diebold (1976) who also tested S factor is difficult to evaluate due to the form of presentation of the data.

Kell blood groups have been studied by Parker et al. (1961), Irvine and Miyashita (1967), Masters (1967), Baker et al. (1977) and Beckman et al. (1978c). Parker et al. (1961) found an increased frequency of the K (+) phenotype among the manic-depressive and psychoneurotic patients as compared to controls. The combined patient material, but not each separate patients group, was significantly different from controls. Patients and controls were from different populations (North Carolina, U.S.A. and England, respectively) which complicates the interpretation. Masters (1967) and Baker et al. (1977) studied the Kell blood group in manic-depressive and psychoneurotic patients and found normal frequencies. The other investigators (Parker et al., 1961; Baker et al., 1977) studied the Duffy system, but found no association with the affective disorders. Beckman et al. (1978c) commented that contradictory findings of the previous workers may be accounted for unstandardised classification of patients.

Shapiro et al. (1977) determined the ABO blood groupings for 66 manic-depressive patients diagnosed and divided into bipolar and unipolar groups according to strict symptomatic and course criteria. A significant higher frequency of bipolar patients than unipolar patients had blood group O, while a significantly higher frequency of unipolar than bipolar patients had blood group A. These findings, according to the authors, support the validity of unipolar and bipolar distinction and are consistent with concept that vulnerability to manic-depressive disorder may be related to membrane disturbances. However, the higher frequency of blood type A in unipolar affective disorder as reported by Shapiro et al. (1977) had not been confirmed by James et al. (1977).

Beckman et al. (1978c) have studied the frequency distribution of ABO, Rh, MNSs, P, Kell, Lewis and Duffy blood groups in a total of 219 patients with affective disorders classified into four groups: bipolar (manic-depressive) psychosis, unipolar recurrent depressive psychosis, non-psychotic 'reactive' depression, and 'unclassifiable'. A significantly increased frequency of blood group factor B among psychotic (bipolar and unipolar) patients compared to non-psychotic patients and an increased frequency of K(+) phenotype among the non-psychotic patients was obtained. Previous results concerning differences between bipolar and unipolar patients with respect to A and O blood groups were, thus, not confirmed in this investigation. This may be accounted for different diagnostic criteria used by these investigators than those of the earlier workers, which may have given rise to contradictory findings.

Lange (1970) studied serum protein groups in manic-depressive patients.
Haptoglobin and post albumin groups were studied by means of starch-gel electrophoresis and Gc serum groups by means of immuno-electrophoresis. No association with the Gc serum groups was found. In manic-depressive psychotics, the frequency of homozygous haptoglobin (Hp 1-1) type was decreased and that of homozygous haptoglobin (Hp 2-2) type increased as compared to the controls. These findings were compatible with those of Beckman et al. (1978b). In the post albumin (PA) system, manic-depressive patients showed a distinct decrease in the frequencies of the PA 1-1 and PA 2-1 types and a corresponding increase in the frequency of homozygous PA 2-2 types (Lange, 1970), however, Beckman et al. (1978) was not able to identify the PA phenotypes of Lange (1970) in affective disorders, but found two statistically significant associations, i.e. increased frequencies of the PGM1 gene in bipolar patients and of the ESD1 gene in reactive patients. No association was found between affective disorders and the Gc and 6-PGD systems.

In an other study, Beckman et al. (1978a) investigated the frequencies of HLA-antigens, blood groups, serum groups and red cell enzyme types in patients with Cycloid psychosis and compared them with those in patients with bipolar psychosis and normal controls. Patients with Cycloid psychosis showed an increased frequency of Rh-negative type as compared to controls, an increased frequency of K (+) phenotype, compared to both bipolar patients and controls, and an increased frequency of the serum group Ge-2-1.

Rinieri et al. (1979) investigated the association between affective disorders and ABO blood types and their study provides the evidence of a positive association between-unipolar affective disorder and blood type A, a positive association between unipolar affective disorder and blood type O : and a positive association between involutional depression and blood type A and a corresponding negative association between the former and blood type B and O. Recently, Singh et al. (1979) have also compared the ABO blood groups of unipolar and bipolar affective disorders with the normal controls, but they could not confirm the previously reported increased frequency of blood group O in manic-depressive psychosis. The bipolar group had a significantly higher frequency of blood group O and a significantly lower frequency of blood group A in comparison to the normal controls as well as the unipolar group. There were no significant differences in the frequency of ABO blood groups between the unipolar group and normal controls. However, their findings supported the distinction between unipolar and bipolar affective psychoses.

Except for four studies (Shapiro et al., 1977; Beckman et al., 1978c; Rinielis et al. 1979 and Singh et al., 1979) where the dichotomy of manic-depressive psychosis has been realized (i.e. division into unipolar and bipolar affective disorders), no other study has taken into consideration the heterogeneity of this illness (Table-1). The over representation of any of the two subcategories, i.e. unipolar and bipolar, may give rise to erroneous findings or the true relationship may disappear. This may be accounted for the inconsistent findings of the above investigators. The non-uniformity of diagnostic criteria and misrepresentative controls used for the investigation may yet be other reasons.

NEUROSES

A few studies have been reported in neuroses in relation to serological and
Table 1. Comparison of Percentage distribution of ABO of blood group phenotypes in Normal Control and Abnormal populations.

| Group               | No. tested | O  | A   | B   | AB  | Source                  |
|---------------------|------------|----|-----|-----|-----|-------------------------|
| Controls            | 12123      | 42.00 | 44.00 | 10.00 | 4.00 |                         |
| Unipolar            | 23         | 22.00 | 65.00 | 9.00  | 4.00 | Shapiro et al. (1977)   |
| Bipolar             | 43         | 70.00 | 23.00 | 5.00  | 2.00 |                         |
| MDP (UP+BP)         | 66         | 53.00 | 38.00 | 6.00  | 3.00 |                         |
| Controls            | 59862      | 40.10 | 44.20 | 10.90 | 4.80 |                         |
| Unipolar            | 90         | 37.80 | 44.20 | 15.60 | 4.40 | Beckman et al. (1978c)  |
| Bipolar             | 51         | 31.40 | 51.00 | 13.70 | 3.90 |                         |
| MDP (UP+BP)         | 141        | 35.46 | 43.39 | 14.89 | 4.26 |                         |
| Controls            | 304317     | 40.90 | 49.20 | 13.90 | 5.00 |                         |
| Unipolar            | 43         | 58.20 | 30.20 | 9.30  | 2.30 | Rinieris et al. (1979)  |
| Bipolar             | 87         | 56.30 | 26.40 | 12.70 | 4.60 |                         |
| MDP (UP+BP)         | 130        | 56.92 | 27.69 | 11.54 | 3.85 |                         |
| Controls            | 12615      | 33.40 | 21.90 | 36.90 | 7.80 |                         |
| Unipolar            | 96         | 38.30 | 19.80 | 37.50 | 9.40 | Singh et al. (1979)     |
| Bipolar             | 104        | 48.10 | 11.50 | 34.60 | 5.80 |                         |
| MDP (UP+BP)         | 200        | 41.00 | 15.50 | 36.00 | 7.50 |                         |

Biochemical characteristics. Maurer Groeli (1974) studied blood groups in psychiatric, organic and psycho-somatic illnesses but did not find any significant relationship with the ABO blood groups and psycho-neurotic depression. A statistical investigation was carried out by Diebold (1975) regarding the distribution of ABO blood groups and Rhesus factor in 920 patients with neurotic disturbances, affective psychoses, Schizophrenia and organic psycho-syndromes with 5000 blood donors serving as controls. In patients with neurotic disturbances, blood groups O and AB predominated together with B and Rh-positive in a bivariate distribution. However, the patients with affective psychoses and Schizophrenic or organic psycho-syndromes were normally distributed. Later in another study Diebold (1976) demonstrated significant differences in the distribution of ABO, Rh and MNSs blood group systems in patients suffering from neurotic disorders as compared to the normal population.

A strong association between hysteria and phenotype A was suggested by Rinieris et al. (1978a). They studied 75 subjects and compared them with controls and found a significantly higher incidence of blood type A which supported the view that hereditary factors contribute to the development of hysteria. In
another study, Rinieris et al. (1978b) determined the ABO blood types in 38 patients with obsessive-compulsive neurosis, 48 Schizophrenics with anancastic symptomatology, 31 depressive with anancastic symptomatology, 260 Schizophrenics free of anancastic symptomatology and 65 depressives free of anancastic symptomatology. These results were compared with a representative sample of general population. The findings provided the evidence of an association between obsessive-compulsive neurosis and phenotype A, while a similar association between ABO blood types and anancastic symptomatology occurring during the course of psychotic disorders was ruled out.

Beckman et al. (1978b) in a serum protein and red cell enzyme polymorphism study found an increased frequency of Hp2 gene and ESD1 gene in non-psychotic reactive depressives.

Recently, phobic neurosis and ABO blood factors were investigated by Rinieris et al. (1980) and the results of the study provided evidence of a positive association between phobic neurosis and blood type O, and a corresponding negative association between the former and blood type A.

These findings together with the previous ones concerning the association between ABO blood types and other neurotic conditions support the view that hereditary factors may contribute to the development of neurotic behaviour.

The limited studies carried out in neuroses allow us to interpret the results with caution, unless a large series of studies are conducted from different centres to arrive at some definite conclusions.

CONCLUSIONS, IMPLICATIONS AND SUGGESTIONS

The foregoing review of the association of various serological and biochemical genetic markers in mental disorders is interesting to the extent that certain polymorphic genetic markers show susceptibility towards psychiatric disorders. The proneness of a marker towards a disease implies the genetic aetiology for that illness. If such a relationship is established, it provides many-fold utility not only in the diagnosis but also in ascertaining the morbidity risk and genetic loading to that illness.

In the present evaluation the inconclusive and inconsistent findings of various investigators may be attributed to various factors like heterogeneity of the disorder, non-uniform diagnostic criteria used, misrepresentative control used, defective statistical analysis, ethnic heterogeneity of the sample, etc. These drawbacks not only lead to erroneous findings, but also make the data incomparable with other studies. The compatibility in as many as aspects results in to draw valid and definite conclusions.

In addition to serological and biochemical investigations in psychiatric disorders, studies have also been reported where the colour blindness, glucose-6-phosphate dehydrogenase (G-6-PD) enzyme deficiency, Xg blood groups, HLA-antigens have been examined for linkage studies and they have also given some clues to understand the mechanisms of transmission of psychiatric disorders. While exhaustive family and linkage studies have been reported from the West, nothing concrete has been done in this direction in the Indian setting. It will be interesting to study the serological and biochemical markers among the relatives of the index cases which help us to ascertain the genetic loading of the mental abnormalities in the families. The consanguineous marriages further increase the morbidity among the mentally disturbed families. The compatibility of genetic load (as revealed by the association of serological/biochemical markers) of both
the parents who are prone to certain
disease may also give rise to proliferate
the defective genome.

Regional variations have been found
regarding the incidence of psychiatric
disorders in the population. The North
and South Indian population differs in
this respect (Raju, 1979; Singh, 1979).
Singh (1979) has suggested a high inci­
dence of psychiatric problems in North­
Western India due to a tendency among
the Punjabis to marry only Punjabis which
gives rise to high incidence of genetically
determined affective illnesses. But in the
South Indian populations where the con­
sanguineous marriages (among the blood
relatives) are more prevalent than among
the Punjabis, the incidence should be
expected to be higher there too, which is
not the case. Since the serological/bio­
chemical traits show affinities towards cer­
tain disorders, it is possible that the high
frequency of certain disease prone genetic
markers may be responsible for the high
incidence of mental disorders in the
North-Western Indian populations.

To conclude, it may be said that gene­
 tic paradigm recognizes the role of intrin­
sic (genetic) factors for individual homeo­
stasis and susceptibility or resistence to a
disease; and medical paradigm empha­
sizes the importance of extrinsic (environ­
mental) factors in the aetiology of a
disease. Since the individuals have their
own genetic signature, it follows from the
genetic paradigm that each person is at
his or her own specific risk for a particular
disease or disorder. Evidence is now
available that in some mental disorders
the expression of a particular gene, or
genes, in a specific environment is respon­
sible for an illness. However, ubiquity of
genetic diversity requires the development
of services for genetic diagnosis, screening
and counselling at each psychiatric clinic
to prevent and treat a major portion of
the mental disorders in the modern
society.

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