

Genetic Regulation and Effect of Age-Sex Variation on Immunoglobulin Levels - An Investigation Based on a Population Study

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ABSTRACT A study of G, A and M immunoglobulin levels in 93 individuals, belonging to Badia population of Malda district, West Bengal, reveals trends of sex and age variation in IgG, and a lower average of IgM level in males than in females. The correlation coefficients between classes of immunoglobulin appear to be absent in females and positively significant among males. The distributional patterns and average IgM levels apparently appears that the genes regulate IgM level are somehow related to sex determining factors. Intercorrelations between pairs of immunoglobulin reveal greater environmental influence among females compared to that in males. The average IgG and IgM levels in this population appears to be low compared to number of other Indian tribes and caste populations. The sibpair correlations in this population are found to be negative possibly due to environmental influence inflate the correlations.

INTRODUCTION

Immunoglobulin (Ig) levels in individuals indicate response to environmental stresses. They vary with nutrition, infections and occupation (Allansmith et al., 1967; Roberts et al., 1979; Al-Agidi and Roberts, 1980; Kumar, 1986a,b). They are higher in tropical than in temperate regions (Kalff et al., 1970; Gupta et al., 1975; Papiha et al., 1980). However, increased IgG, IgA and IgM levels in ethnic Africans and Indians compared to ethnic Europeans inhabiting similar climatic zones of Europe and America (Cohen et al., 1961; Grundbacher, 1974; Maddisson et al., 1975; Riches et al., 1980) suggest genetical influence on immunoglobulin level. This is supported by twin and

family studies (Allansmith et al., 1969; Billewicz et al., 1974; Grundbacher, 1974; Al-Agidi, 1980; Barbosa et al., 1981; Kohler et al., 1985). The suggestions of autosomal genes for IgG and IgA (Lichtman et al., 1965; Kunkel et al., 1969), genes for IgM in X-chromosome (Grundbacher, 1972), level of IgM is affected by X-linked gene (Kacprzak-Bergman, 1994), and sex-specific factors modifying the regulation of IgM level (McGue et al., 1989, 1990) require verification in other populations. There is also some uncertainty about the exact nature of age and sex differences in IgG and IgA levels (Grundbacher and Shreffler, 1970; McFarlane, 1973; Al-Agidi, 1980; Clark et al., 1981).

This paper examines the trends of age and sex variation in the levels of these three types of immunoglobulin in a series of families from a local endogamous population of West-Bengal, India, and attempts to verify the earlier suggestions of genetical influence on them.

MATERIALS AND METHODS

Population Study

The Badia, an endogamous Muslim population reside in low and marshy land in the rural areas of Malda district, West Bengal. Their huts are linearly arrayed, parallelly faced in opposite direction of muddy roads. They live in shabby, less ventilated and over crowded small mud-built houses. Practice of consanguineal marriages are common amongst them. They are economically poor Bengali speaking agricultural people and they belong to La Ma-

jhabi sect of Islam. Their ancestors are suspected to have migrated from Afghanistan during the middle of sixteenth century as soldiers of Sher Shah. Little is known about the disease stress among the agricultural Badia population. On the basis of available preliminary information it can be stated that tuberculosis in adults and enteric diseases in young children are the major health concern. Blood samples were drawn in heparinised capillaries from 47 males and 46 females, aged between 4 and 76 years, individuals belonging up to 3 generations of 15 families. Pregnant and menstruating women were not included in the study. Ages were estimated by applying standard anthropological methods.

Immunoglobulin Estimation and Statistical Analysis

IgG, IgA and IgM levels were measured by radial immunodiffusion technique (Mancini et al., 1965) with the help of tripartigen plates

supplied by Hoechst Pharmaceuticals along with the stabilized standard serum. Statistical methods applied include (1) Student's t-test to determine age differences in mean immunoglobulin levels, (2) Multivariate analysis was performed to regress out effects of age and sex on the trait, and intra-class sibpair correlations using ANOVA test, correlations between classes of Ig, and (3) Mann-Whitney U-test to determine sex differences in Ig levels. BMDP and MINITAB packages were used to perform the tests.

RESULTS

Descriptive statistics of IgG, IgA and IgM concentration in different age-groups and sexes are presented in table 1. An overall consistent trend of increase with age in IgA level in both sexes; a small increase in IgG level upto adolescence in males and third decade of life in females; an increase in IgM level upto third

Table 1 : Age and sex differences in immunoglobulin levels

Age in years	n	Immunoglobulin levels (mg/100ml)					
		IgG		IgA		IgM	
		Mean	SE	Mean	SE	Mean	SE
<i>Male</i>							
< 10	7	1331.30	149.16	131.82	28.05	161.89	5.74
10-19	18	1464.17	110.54	175.83	18.24	140.82	12.59
20-29	12	1243.75	128.74	188.96	33.96	132.12	12.57
30-39	5	1240.00	193.91	193.10	38.52	111.95	23.05
40-49	2	1312.50	37.49	189.75	0.00	191.07	44.43
> 50	3	1550.00	139.19	195.33	29.01	104.93	11.45
All Ages	47	1378.00	62.87	176.30	12.55	138.72	6.67
<i>Female</i>							
< 10	7	1457.14	172.15	130.61	17.64	172.83	19.63
10-19	14	1684.57	138.52	150.28	11.30	176.76	15.29
20-29	8	1821.43	201.79	207.03	27.21	229.03	23.89
30-39	10	1447.50	72.50	203.70	26.68	199.96	20.08
40-49	4	1631.25	194.55	205.56	17.31	178.08	39.57
> 50	3	1625.00	108.97	222.17	30.07	190.64	54.06
All Ages	46	1610.11	64.22	178.26	9.71	191.32	9.32
Male + Female	93	1492.00	46.21	177.27	7.90	164.73	6.28
<i>Log-transformed Values</i>							
Male all ages	47	3.115	0.022	2.191	0.033	2.121	0.019
Female all ages	46	3.191	0.016	2.218	0.026	2.252	0.023
Male + Female	93	3.152	0.014	2.204	0.021	2.186	0.016

decade of life only in females; and on the contrary a decline with age in IgM level among the males, apart from small sampling fluctuations, have been observed in the present series of data despite its small sample size. In females, mean levels of IgG approximately 17% and IgM 38% are higher than that for males. Decline with age in average IgM is found to be significant in third decade ($t=2.15$; $p<0.05$) compared to that in first decade of life. Effect of three independent variables, family level, age and sex, on each classes of immunoglobulin (IgG, IgA and IgM) - dependable variable, have been ascertained by performing ANOVA test. Inter and intra family variations in all the three classes of Ig have been found to be non-significant at 5% level of probability. Significant effects of age only on the variability of IgA ($F_{3,27} = 1.62$; $p<0.05$), and sex on IgG ($F_{1,91} = 6.70$; $p<0.01$) and on IgM ($F_{1,91} = 21.28$; $p<0.001$) levels have been found. Non-parametric, Mann-Whitney (U) test statistic, also yield significant differences in IgG ($U=802.00$; $p<0.03$) and in IgM ($U=536.00$; $p<0.001$) levels.

Distribution of IgG, IgA and IgM across the sexes (Fig. 1) reveal that the entire range of IgG and IgA levels tend to shift towards higher values in females than that in the IgM levels in males. While IgM levels in males occur in greater frequencies of relatively low levels of IgM than that of females.

Since, the coefficients of skewness and kurtosis of the dependent variables IgG, IgA and IgM have been found large and significant at 5% level, the logarithmic transformed values for each sex and for the total sample are given in table 1. Regression analysis has been performed for each log-transformed, log-IgG, log-IgA and log-IgM levels with predictor constant age in each sex separately and also predictor variables sex and age in total sample to remove effects of age and subsequently sex on those dependent variables. The predictor variable age had significant effect only on log-IgG (t-ratio for sex = 2.75; d.f. 2,90; $p<0.007$) and on log-IgM (t-ratio for sex =

4.60; d.f. 2,90; $p<0.000$). Correlation coefficients among the three dependent variables, after making adjustments with predictor variables, significant phenotypic correlations between pairs of Ig are obtained only among the males and none of the correlations are found to be significant among females (Table 2). Even after adjustment for effect of sex in the total sample the correlation between log-IgG-log IgM remain to be non-significant.

Table 2 : Phenotypic correlations (r) between classes of immunoglobulin concentrations

Immunoglobulins	Male n = 47	Female n = 46	Total n = 93
log-IgG - log-IgA	0.727 ¹	0.272	0.575 ¹
log-IgG - log-IgM	0.321 ²	-0.027	0.157
log-IgA - log-IgM	0.322 ²	0.252	0.282 ²

1. $p < 0.001$ for difference from zero

2. $p < 0.05$ for difference from zero

The coefficients of correlation between sibpairs are computed on log-transformed and adjusted for age data (Table 3). These correlation values between pairs of sibs do not fit with any

Table 3 : Correlation between sibpairs

Immunoglobulins	Pairs of relatives		
	Brother:Brother (n = 34)	Sister:Sister (n = 17)	Brother:Sister (n = 51)
IgG	-0.2671	-0.1580	-0.0076
IgA	-0.4745	-0.4795	-0.4561
IgM	0.0252	0.1985	0.3669

of the common genetic models. Within sibpairs (male, female and male-female) variation in IgG and IgA are found to be larger compared to those in between pairs, and are significant in IgA level among male pairs ($F_{14,19} = 2.81$; $p<0.02$) and male-female sibpairs ($F_{14,36} = 2.64$; $p<0.009$) while in IgM between variations are larger than that in within variations. In order to measure proportional amount of X-linked influence in correlations produces by multifactorial traits, which is independent of dominance, following index of Penrose (1971) has been applied :

$X_{bb} = 2(r_{bb}r_{tt} - r_{bt}^2)/(r_{bb}r_{tt} + r_{bt}^2)$ where bb refers to brother-brother; tt to sister-sister; and bt to

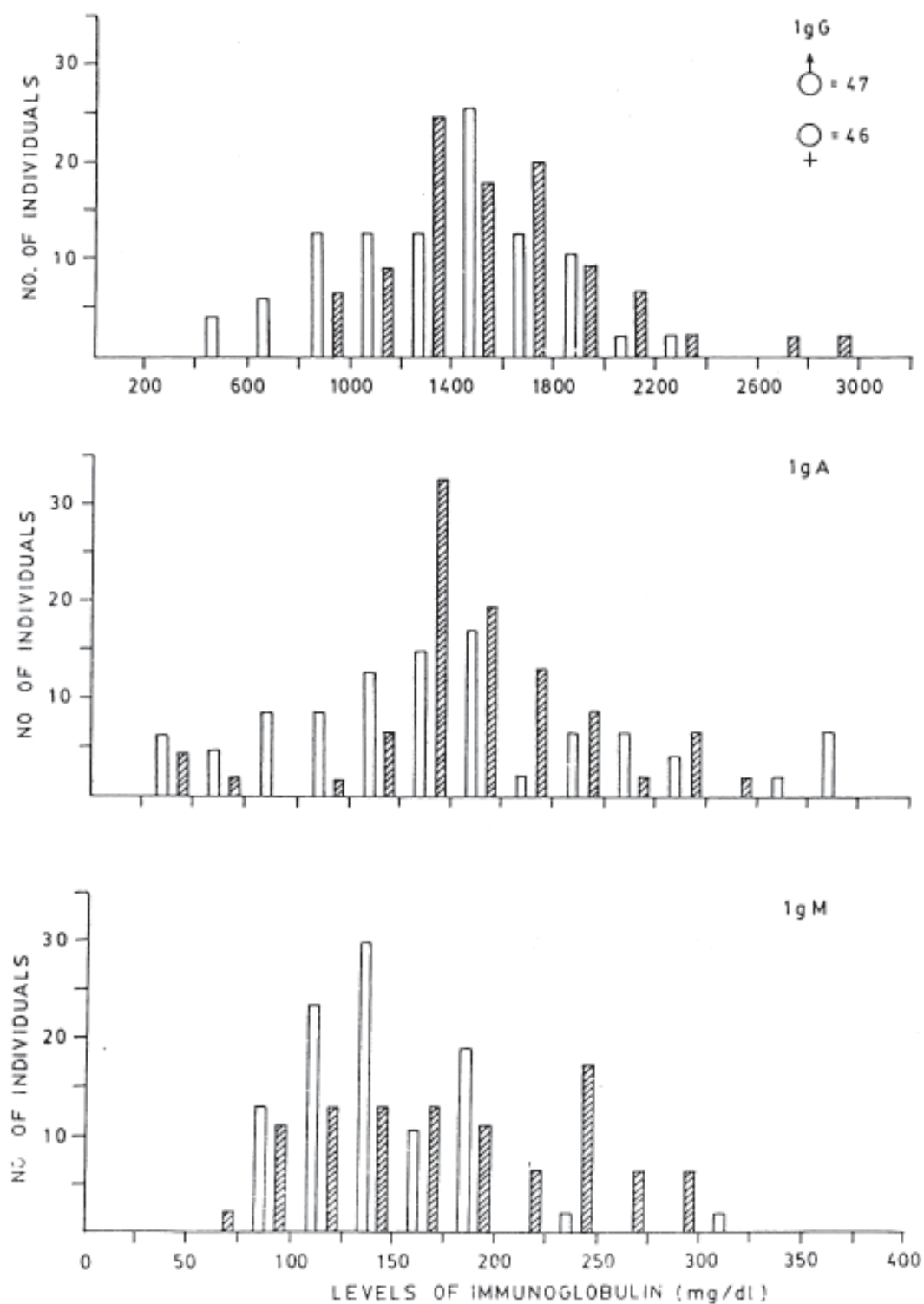


Fig. 1. Distribution of Ig levels in sexes, hatched bars for females and white bars for males

brother-sister correlations. In perfectly additive conditions all these estimates of sex-linked hereditary influence should vary between zero and +1. But neither of the results obtained on IgG nor IgM provide information for X-linked genes responsible for quantitative variation in the present series of data.

DISCUSSION

A comparison of immunoglobulin levels according to sex indicated a significantly higher levels of IgG and IgM in females than that in males. This significantly higher levels IgM in females have been reported in many other studies (Allansmith et al., 1968; Clark et al., 1981; Kacprzak-Bergman, 1994) and subsequently suggestions were made that the trait is affected by X-linked gene(s), by dosage effects of X-chromosome (Rhodes et al., 1969; Wood et al., 1969), by familial correlations (Grundbacher, 1972, 1974), and by finding greater phenotypic variance in male twins than that for female twins (Kacprzak-Bergman, 1994). This hypothesis has, however, not supported by work of the following authors, Guizer-Vazquez et al. (1977), Escobar and Bixler (1979), Clark et al. (1981), and McGue et al., (1990). The results of IgM concentration and between the number of X-chromosomes is in fundamental disagreement with Lyon's hypothesis (Lyon, 1961). This study do not reveal X-linked gene(s) in controlling levels of any classes of immunoglobulin. The evidence for gene dosage effect in human is still equivocal on the ground that such correlated enzyme activity changes do not occur in all cell types (Thompson and Thompson, 1973), they occur even when the gene in question is not located on the involved chromosome (Hsia et al., 1968; Sellyer et al., 1969). Some studies have also shown slightly higher levels of IgG in females than that for males (Grundbacher, 1974; Clark et al., 1981; Kacprzak-Bergman, 1994) and also significantly higher levels of IgA in males than that for females (Clark et al., 1981). The sex difference in IgG and IgM lev-

els are found to be larger in the population under study than those observed by Grundbacher (1972, 1974) among American Whites and Blacks; Roberts et al. (1979) among African populations; and Kumar (1986a; 1986b) among some Indian populations. Further, similar pattern in intra-pair variance and genetic variance distribution across sexes in different classes of Ig have been reported among Polish monozygotic and dizygotic twins (Kacprzak-Bergman, 1994).

Average IgG and IgM, for the total sample appear to be higher and IgA to be lower than those reported for Europeans, Arabs Kurds (Al-Agidi and Roberts, 1980), Tibetans (Gupta et al., 1975), and IgG among Brahmins of Madhya Pradesh, India (Papiha et al., 1980). All the three classes of immunoglobulin are found to be much lower than the reported nine populations representing three different states of India and which include some isolated tribal populations along with Hindu and Muslim population (Papiha, 1990), and a few tribes of Central India (Das and Das, 1995). However, IgG level in the present series is also found to be lower than that in the Iranian populations (Paphia et al., 1987), Bengali population (Kumar, 1986), and three Koch populations of north West Bengal (Das et al., 1995).

Age effects on IgA levels has been found to conform with some reported studies (Buckley and Dorsey, 1970; Grundbacher, 1974; Maddison et al., 1975) but the trend of increase in IgG levels is observed to be prolonged in the present series while other studies have revealed only a rapid increment only in early childhood (Alfred, 1971; Buckley and Dorsey, 1970).

Besides genetic architecture in the control of immunoglobulin synthesis environmental challenges play vital role to represent dynamic equilibrium between the rates of synthesis and catabolism of these proteins, such occurs for IgG by renal or gastrointestinal protein loss (Rowe et al., 1968), for IgA respiratory infections (Thompson, 1977). On the other hand, the elevated levels of immunoglobulins may be due

to increased synthesis of protein, under the antigenic stimuli following exposure to various parasitic and infectious agents, for example, high levels of IgM have been negatively correlated with malaria (McGregor et al., 1970; Kunal et al., 1979), increased IgG level work as an enteric antiviral infection (Yolken et al., 1989, 1990) and further Kalff and Hizmans (1969) observed significantly higher intra-pair variance among MZ twins who had lived apart for more than one year than those twins who lived together. Negative sibpair correlations observed in the present series in which within variances are larger compared to that between pair variances in IgG and IgA levels.

Sex difference in phenotypic correlation between different classes of Ig in the present series reflects males have both greater genetic and environmental control for synthesis of different classes of Ig than that in the females. Females have larger encosensitivity of IgG and IgM levels which enhances adaptability to varied environmental conditions than the males. Suggestion of greater resistance to certain infections in females than in males (Washburn et al., 1965; Grundbacher, 1972) also gets support from the present finding. Furthermore, some authors have reported heritabilities for sexes separately and Rowe et al. (1968) found greater genetic control of IgG in adult males than that in the females; Clark et al. (1981) observed greater genetic control of IgA in males than females; Kacprzak-Bergman (1994) observed higher heritability in IgG among males than females and conversely greater heritability of IgA in females than males.

In the present study a slightly stronger genetic regulations of IgG and IgM in males than females can be suggested. It is generally known that heritability coefficient can differ in various population. What factors could be responsible for the greater environmental variability in females than that in the males remains to be answered. The explanation can be provided by endocrinological and immunological data. Some observation suggest sex-hormone and

pituitary hormone influence antibody response through various mechanisms (Stoecker et al., 1988; Abas, 1989; Athreya et al., 1993). However, deviations in sibpair correlations from that expected in additive genetic model observed in present series of data may largely be attributable to environmental causes. The coefficients of correlation between brother-sisters are found to be larger than sisters which do not follow X-linked model. Nevertheless, the coefficients of correlation between pairs of relatives or twins are widely applied in genetic analysis to estimate magnitude of genetic component. The reliability have been challenged by Garn et al. (1976) that adoptive parent-offspring correlations are not significantly lower than those for biological parent offspring pairs for traits such as height, weight, skinfold thickness etc. Obviously a new approach is necessary to resolve the subject of this discussion.

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