Anthropological Significance of Alloalbuminaemia

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INTRODUCTION

Alloalbuminaemia (a term coined by Blumberg, 1969) is the presence in human serum of a form of albumin distinguishable from normal serum albumin mainly by charge induced alterations in its electrophoretic mobility (Shrivastava et al., 1972).

Since the discovery of first case of alloalbuminaemia in 1955 by Sheulren, more than 100 genetic variants of the protein bearing different ethnic and geographical names have been reported (Galliano et al., 1990). The identification has been done either by clinical electrophoresis in the sera of the patients or blood donors or by genetic screening using a series of electrophoretic methods. Quite a few among these have been subjected to structural studies. The structural analyses conducted on approximately 35 different genetic variants of human serum albumin have shown most of these variants to differ from each other by single amino acid substitutions probably due to point mutations in the gene (Schell and Blumberg, 1977; Fine et al., 1987 and Madison et al., 1991). Takahashi et al. (1987) and Minchiotti et al. (1987) have listed about twenty different amino acid substitutions and nucleotide mutations. These investigations were further stimulated by the availability of advanced technology.

Serum albumin polymorphism is very rare in most human populations but does occur with a prevalence of more than 5% in certain ethnic groups, particularly in north and south American Indians (Weitkamp et al., 1973; Schell et al., 1978; Putnam and Takahashi, 1987).

Albumin variants have shown balanced polymorphism in certain American Indian groups for example albumin Naskapi has been reported to occur with high frequencies (0.130) in the Naskapi Indians of Quebec (Johnston et al., 1969; Schell and Blumberg, 1977) and a linguistically different Algonkian speaking people of eastern United States and Canada. Similarly Mexico-2 (Melartin et al., 1967) showed polymorphic frequencies in Pima Indians of the Gila river community near pheonix, Arizona (Takahashi et al., 1987b) and albumin B, in European populations (Earle et al., 1958).

ANTHROPOLOGICAL SIGNIFICANCE OF IDENTICAL SUBSTITUTIONS IN ALLOALBUMINS

A number of albumin variants of slow as well as fast electrophoretic mobilities have been reported in Indian populations.

(i) Ethnic and Geographic Distribution of Albumin Kashmir: The most commonly observed variant in Indian populations turned out to be albumin Kashmir. The structural analyses (Tarnoky, 1980) revealed the occurrence of alterations in cynogen bromide fragment, CB6 in nine named alloalbumins i.e., albumins Ropar, Punjab, Kashmir, Vancouver, Birmingham, Adana, Lambadi, Manaus I and Porto Alegre II) identified in unrelated individuals of diverse ethnic origin and living in different continents. Seven of these clearly have an Asiatic origin : Ropar (Mehta, 1994), Punjab (Kaur et al., 1982), Kashmir (Tarnoky and Dowding, 1969), Lambadi (Walter et al., 1980) in north India, Vancouver (Huss et al., 1988b) and Birmingham (Bradwell et al., 1975) present in unrelated families which migrated from Uttar Pradesh (U.P.) and Punjab respectively, and Adana in Turkey. Porto Alegre II was reported from a Brazilian of African/ Caucasian (Portuguese) ancestry, whereas racial backround of Manaus I is unclear. The structural work conducted in seven of these alloalbumins showed the same amino acid exchange at position 501 where glutamic acid was replaced by lysine. This substitution 501 Glu—>Lys accounted for the slow +2 electrophoretic mobility and was attributable to a point mutation in codon GAG to AAG.

The presence of same amino acid exchange in the above mentioned alloalbumins with an Asiatic origin shows that these may have arisen from an early common ancestor in the vicinity of northern India. Despite the names - Kashmir, Birmingham, Vancouver - each detected in a different continent, the gene for these alloalbumins originated in Asia. Since Kashmir, Punjab and Uttar Pradesh are neighbouring states in northern India, Schell and Blumberg (1977) concluded that “albumin kashmir” is restricted to families of Indo-Dravidian descent, but it occurs more often than any of the other

restricted variants. According to historical and other information, north of India was repeatedly invaded by Afghans, Moghuls, Turks and Arabs hence it appears reasonable to postulate that some of the albumin variant genes like albumin Kashmir were introduced during these invasions or alternatively the presence of Kashmir like variant i.e. albumin Adana in Turkey was introduced by the women who were taken away from the Indian region by the invaders along with the 'loot'. The Punjabis themselves are known to have descended from early Aryan settlers who migrated from central Asia, entered India on the north-western border and established themselves in Punjab (Rose, 1970). They avoided union with other aboriginal populations. The albumin Kashmir gene may have been introduced by this group. These observations have tremendous significance with respect to the criteria for typing albumin variants and for ethnic and geographic distribution of this and other variants.

However, the occurrence of Kashmir like variants in Brazilian populations appear to have had an independent mutation at the locus for albumin gene.

(ii) Ethnic and Geographic Distribution of Albumin B: First case of albumin B from India was reported by Kaur et al. (1982) and was originally designated as albumin Sirhind. From Europe a large number of albumin B variants bearing different names such as albumins Oliphant, Ann Arbor, London, Lubeck, Verona and a few undesignated ones have been found in published reports. Five cases of albumin B named as albumins Osaka-2 (Ara et al., 1990), Nagano (Arai et al., 1990), Tokyo-1, Shinanomachi-1 (Arai et al., 1989a), and Saitama-1 (Arai et al., 1989b) have been reported from Japan and one case designated as Phnom Penh from Cambodia. All the variants of B type have been found to have amino acid substitution site at position 570 with the replacement of glutamic acid by lysine (570 Glu → Lys). This substitution accords with a change in electrophoretic mobility of +2 where the codon GAG is changed into AAG with the replacement of G → A.

The apparent presence of albumin B in north India indicates that this gene is not restricted to European populations alone as it previously appeared to be. It may have been introduced by the British who first entered India in 1599. India after 1857 was totally under British rule till 1947. Some population admixture is known to have occurred during this period. Alternately, it may have arisen as an independent mutation in the Indian subcontinent.

Presence of albumin B in European populations may also be explained on the basis of consanguinity. In the most extensive study of the inheritance of albumin B, Frohring in 1985 (c.f. Arai et al., 1989a) identified it electrophoretically in five generations and traced the genealogy of 63 heterozygous carriers (A/B) to 117 direct ancestors over 14 generations and four centuries. Thus albumin B must have appeared in this kindred before 17th century. The European alloalbumins might in each case be ascribed to a common ancestral gene widely dispersed, perhaps through the Roman migrations. This indicated that the albumin B mutation has occurred a number of times in different populations, and it suggests that the site is hypermutable (Arai et al., 1989a). Another possibility is that certain mutated sites in the albumin gene are more subject to selection than other sites.

(iii) Ethnic and Geographic Distribution of Albumin Naskapi: Another example of identical substitution is the presence of Naskapi like variants, which occurs with polymorphic frequencies in north, south and central American Indian tribes (Schell and Blumberg, 1977), in Eti Turks designated as albumin Mersin (Franklin et al., 1980b), in Indian populations, albumin Khanna (Kaur et al., 1982) and in a single Japanese designated as albumin Komagome-1 (Madison et al., 1991) all having the same amino acid substitution site at position 372 where glutamic acid is replaced by lysine (372 Glu → Lys). The incidence of Naskapi like variants could be attributed to mutation, that either occurred in an ancient population ancestral to both American Indians and Asian groups like Eti Turks, Indians and Japanese or was introduced by subsequent admixture from descendants of this ancestral population. Alternatively, the variants from Asia may have arisen by independent mutations and thus bear no direct relationship with these population groups. On historical grounds population admixture is a reasonable explanation.

Modern Turkey was in antiquity part of the eastern (Byzantine) Roman Empire, and historians of the period have provided extensive documentation of nearly continuous invasions of the area by nomadic people of central and east Asian stock. During the sixth through ninth centuries, the Byzantines alternatively allied with and fought with a number of groups, in-

cluding the Avars and Khazars. In the 11th, 13th and 15th centuries, Asia minor was successively conquered by the Seljuks, Mongols and Ottomans, all of whom were of Asian origin (c.f. Franklin et al., 1980b). Most of these conquerors were relatively few in number and formed a ruling elite that was eventually absorbed into the indigenous population. The presence of albumin Naskapi may be one of the few detectable indicators of gene flow from Asia.

(iv) Ethnic and Geographic Distribution of Some Other Variants: Abumin Reading with amino acid substitution 313 Lys → Asn, is the second most frequently observed one in European populations (Tarnoky and Lestas, 1964). Similar amino acid substitutions have been found in albumin Cooperstown (New York), albumin Tagliacozzo (Italy), albumin Canterbury (NewZealand) IRE (Sakamoto et al., 1991) in a case from Sweden reported by Carlson et al. (1992) and in albumin New Guinea from New Guinea Indigenes where it approaches polymorphic frequencies.

Some other examples of independent mutations include the amino acid exchange 550 Asp →Gly reported in albumin Mexico-2 from Mexico and also from Sweden (Carlson et al., 1992) independently. Similarly, amino acid substitution 365 Asp→His has been found in albumin Parklands from New Zealand (Brennan, 1985) and albumin Iowa city-1 from America (Madison et al., 1991) and presence of amino acid substitution 563 Asp→Asn in albumin Fukuoka-1 and albumin Ube-1 from Japan and in albumin Paris-2 from Europe.

A similar case of having same amino acid exchange at position 376 Glu→Gln present in albumin Tochigi from Japan and a single case having same substitution have been reported from Sweden. All these examples indicate independent mutations.

(v) Ethnic and Geographic Distribution of some Restricted Variants: A number of Alloalbumins restricted to particular ethnic group or geographic region have been found in Italy, Torino, Vibo Valentia, Roma, Vanves, Redhill, Castel di Sangro, Milano fast, Catania, IRE2 , Herborn, Sondrio and Venezia. Among these, Venezia, Catania and Milano fast have been detected in a number of unrelated subjects. These variants are almost entirely segregated to specific regions, and may be attributed to isolation in the past.

The presence of homozygotes for albumins Venezia, Catania and Milano fast suggests a founder principle or genetic drift within a restricted population. Indeed, homozygotes for alloalbumins are rare except in certain north American Indian tribes that exhibit a polymorphism (Takahashi et al., 1987a), or in the minimally admixed south American Indian tribes that have "private variants" (Takahashi et al., 1987c). Three Amerindian mutants,Yanomama, Maku and Mexico, characterised by structural study, have not been detected in other racial groups, but Oriximina and Mura-1 have been found to have similar substitution as in Maku i.e. 541 Lys → Glu and one case of albumin Mexico has been reported from Sweden having the same amino acid substitution localized at position 550 Asp → Gly as in albumin Mexico.

Similarly a set of albumin variants detected in Japanese i.e. albumin Nagasaki-1, Niigata, Nagasaki-2, Nagasaki-3, Hiroshima-1, Hiroshima-2, Komagome-2, Osaka-1, Nagoya, have not been detected in other racial groups. Based on the results of extensive electrophoretic surveys with several pH systems in both Japan and Italy, we conclude that at least, in these countries there is no evidence of overlapping in the incidence of these sets of alloalbumins. Substitution, 358 Glu →Lys in Porto Alegre-I and Coari-I have been reported only from Brazil and not from any where else.

KEY WORDS Alloalbuminaemia. Amino-acid. Substitutions.

ABSTRACT The occurrence of point mutations at the same site in the albumin molecule in widely different population groups prompted us to trace the origin and affinities of the variants concerned and draw conclusions about their anthropological significance.

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