Transferrin C subtypes in different ethnic groups and spontaneous abortion

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INTRODUCTION

Schade and Caroline discovered transferrin (Tf), one of the most important members of the iron-binding class of proteins of human plasma, in 1946 (Schade and Caroline 1946). Other members of this class include lactoferrin and ovotransferrin or conalbumin. Tf, sometimes also referred to as sirophilin or serotransferrin is part of the ß-globulin fraction of serum proteins. Tf is synthesized predominantly in the liver and its vital function is to tansport iron from the intestinal sites from cells in which the metal is absorbed, stored, or recovered from senescent red cells, to the cells in which iron-contained molecules are synthesized, such as the proerythroblasts of the bone marrow (Cleve et al. 1988). Transferrin has two binding sites for iron, with slightly different physical and chemical properties. Normally, serum Tf is only one-third satured with iron. Under these conditions it may protect against infections by a variety of microbial species by successfull competing for ferric iron essential for their growth: the free iron-binding sites compete with the siderophores of invading bacteria and fungi (Weinberg 1974). In addition to its function in nutrient binding and transport, Tf has also been suggested to act as a circulation growth factor in proliferation during embryogenesis (Ekblom et al. 1983). Genetically determined electrophoretic variation in the Tf present in human serum was first reported by Smithies (1957) using stach gel electrophoresis for separation. The common Tf type was designated Tf C, and 9 anodal variants and 12 cathodal D variants had been distinguished by 1975 (for review see Walter 1975). Until 1978, Tf C was considered to be a single variant. However, using isoelectric focussing, (IEF) Kühnl; Spielmann and Thymann (1978) independently described two common subtypes, Tf C1 and Tf C2. One year later Kühnl and Spielmann (1979) described another common C variant among Europeans, Tf C3. Family studies indicate an autosomal codominant inheritance of these alleles and recently the Tf locus has been assigned to human chromosome 3q21-q26 (Yang et al. 1984). Subsequently, IEF has revealed some additional heterogenety in Tf C and the total number of C variants has now reached 16 (Kamboh and Ferrell 1987; Kornhuber and Kühnl 1986). Nothing is known so far about the selective forces which may maintain the C1-C2-Cx polymorphism. With the discovery of the Tf C subtypes this problem attracted renewed interest, and various interesting observations were made: Beckmann et al. (1980) observed an increased frequency of the Tf C2 subtype in mothers with spontaneous abortion; Auconi et al. (1982) found a significant increase of the Tf C2 allele among premature newborn infants born before the 32nd week. Beckmann et al. (1985) reported the association of the Tf C2-1 and C2 phenotypes in factory workers afflicted with an occupational photodermatosis presumed to be due to toxic substances released unintentionally from a powder paint with epoxypolyester resign. The same group also reported a significant association of the C2 type with rheumatoid Arthritis (Dahlqvist and

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Beckmann 1985); they proposed a hypothesis that the Tf C2 gene confers an increased risk for cellular damage by hydroxyl radicals.
A review of the literature shows that Tf is one of the most intensively studied systems by IEF and data are available from more than 125 populations from quite diverse geographical areas (Beckmann et al. 1980; Kamboh and Ferrell 1987; Rodewald et al. 1988).
The purpose of our study was to re-examine the relationship between Tf subtypes and spontaneous abortion. In addition to the Tf C alleles there are some other Tf alleles whose distribution is of significance in anthopologigal genetics and therefore we will discuss them too.

MATERIAL AND METHODS

Transferrin subtypes were studied in 75 women from Western Germany with a history of previous abortion. The serum samples were desialylated and subjected to IEF in the pH-range of 4-6.5 (Kühnl and Spielmann 1978).

RESULTS AND DISCUSSION

The distribution of Tf allele frequencies in different populations are given in Table 1. The two common alleles Tf C1 and Tf C2 are present in all populations studied. Generally, the Tf C1 is higher in Blacks, Micronesians, Polynesians, Melanesians and Australian Aborigines, ranging from 80% to 95%, the maximum being found in Micronesian groups. Europeans and American whites have similar frequencies and their distribution falls in the range of 75-78%, but is slightly higher in Australian whites (82%) and in Northern Germany (84%). The minimum value in South Asian populations have been recorded of Bali (50%).
The distribution of the Tf C2 allele frequencies is somewhat reciprocal to that of the Tf C1 allele. The lowest values of Tf C2 have been found in some Amerindian groups (1%), Pygmies in Africa (3%) and Micronesians and Melanesians (4-5%). In European populations the range of Tf C2 frequencies is 13-19%, and in Asian populations the range is extended to 15-34% (Table 1). The maximum values (34%) have been reported in one Indian tribal population and in two genetically isolated groups from Indonesia, and these high C2 frequencies are probably due to genetic drift or founder effects.
Tf C3 appears to be very usefull in population-genetic studies. It is present in 3-7% of European, American and Australian whites and with a slightly lower frequency in 1-4% of Asiatic populations. The discovery of the Tf C4 allele at higher frequencies in New World Amerindian populations clearly demonstrated that this is a marker of these indigenous groups. Most of the remaining Tf C alleles , C5 - C13, are rare and show restricted ethnic or geographic distribution.
The two most frequent variants of Tf D allele were D1 (in Africans, range to 3-15% and in Aborigines 5%) and D chi (in Chinese, Filippinos, and South Indian populations), as a marker of Mongoloid populations.
Table 2 shows the transferrin C subtypes of women with previous abortions and the controls. Among these women significantly increased frequency of the C2 allele and especially of the C2 phenotype was found. There was also a significant departure from the expected Hardy-Weinberg equilibrium in the women as indicated by chi square value. The results of this study were in agreement with previous observations of the study of Beckmann et al. (1980). There appears to exist a selection mainly against fetuses with the C2 phenotype. It is obvious that the mechanism behind a selection mainly against the C2 type can be due to an immunological incompatibility between mother and fetus. Evidence in support of this possible selective mechanism

Table I Distribution of transferrin allele frequencies in different populations

Population	N	Tf allele frequencies C1	C2	C3	C4	D1	Dchi	others	
EUROPE									
Southern Germany	1108	0.79	0.13	0.07	-	-	-	<0.01	Weidinger et al 1984
Northern Germany	869	0.84	0.16	-	-	-	-	-	Jansen et al 1981
Hessen	876	0.77	0.16	0.06	-	-	-	<0.01	Kühnl et al 1981
Sweden Umeá	1084	0.82	0.16	-	-	-	-	<0.01	Beckmann et al 1980
Italy Rome	1352	0.76	0.18	0.05	-	-	-	<0.01	Pascali & Auconi 1983
NORTH AMERICA									
USA Whites	947	0.77	0.16	0.05	-	-	-	0.01	Dykes et al 1982
USA Blacks	386	0.84	0.12	<0.01	-	0.03	-	-	Dykes et al 1981
Amer-indians Apache	140	0.81	0.01	-	0.18	-	-	-	Dykes et al 1982
AFRICA									
Black Nigeria	131	0.86	0.05	-	-	0.08	-	-	Beckmann et al 1980
Pygmy Bi-Aka	337	0.82	0.03	-	-	0.15	-	-	Constans et al 1981
South Africa	426	0.90	0.09	0.01	-	-	-	-	Walter et al 1983
Mocam-bique	82	0.82	0.10	-	-	0.07	-	-	Rodewald et al 1988
ASIA-INDIA									
North I. Vaish	62	0.55	0.34	0.11	-	-	-	-	Kamboh 1984
South I. Konda Kammara	118	0.65	0.25	0.01	-	-	0.09	-	Walter et al 1981
N.W.I. Kotwalia	92	0.85	0.15	-	-	-	-	-	Walter et al 1983
Indonesia Bali	290	0.50	0.34	-	-	-	0.01	0.14	Brequet in Kamboh and Ferell 1987
Filip-pines	107	0.81	0.16	-	-	-	0.03	-	Walter et al 1983
China	118	0.74	0.24	-	-	-	0.01	-	Kamboh and Kirk 1983
AUSTRALIA									
Whites Adelaide	400	0.82	0.15	0.03	-	-	-	0.01	Nicholls & Mulley 1982
Aborigines Central	366	0.90	0.03	-	0.01	0.05	-	0.01	Kamboh and Kirk 1983
Polynesia Samoa	227	0.90	0.09	0.01	-	-	-	<0.01	Kamboh and Kirk 1983
Micro-nesia	411	0.95	0.04	<0.01	-	-	-	-	Kamboh and Kirk 1983
Papua New Guinea	196	0.88	0.08	-	-	0.04	-	-	Kamboh and Kirk 1983

associated with the Tf C2 gene was provided by Auconi et al. (1982) who also observed a significant increase in the C2 frequency among extremely premature infants. Explanations for these observations have generally involved also the possible protective effects of certain Tf alleles against microbial infection or differences in the fetal growth-promoting effects of transferrin. Recently a special function of transferrin as a general growth factor in mammalian cells and particularly in the regulation of proliferation of cells of the immune system were recognized. Bryan and Leech (1983) have demonstrated the immunregulatory effects of Tf. Lum et al. (1986) suggest that Tf, synthesized by inducer T lymphocytes, acting in concert with the Tf receptor system, represents an autocrine pathway of potential importance in embryonic development and in immunregulation.
The further definition of the role of the Tf-Tf receptor system in the regulation and stimulation of the immunological system and in cellular proliferation and embryonic development generally should stimulate investigation into the biological function of transferrin genetic variation.

Table II Distribution of transferrin C subtypes in women with and without spontaneous abortion

	our study				Beckman et al. 1980			
	women with previous abortion		Controls Weidinger 1982		women with previous abortion		Controls	
Tf	N	%	N	%	N	%	N	%
C1	46	61.33	330	73.33	88	61.1	248	71.5
C1-2	24	32.00	101	22.44	45	31.3	88	25.4
C2	5	6.67	11	2.45	11	7.6	11	3.2
C1B1			1	0.22				
C1B1-2			2	0.45				
C1B2			4	0.89				
C1D1			1	0.22				
	N=75		N=450		N=144		N=347	
RR for C1 =0.54	TfC1=0.7733		TfC1 =0.8544		TfC1=0.7670		TfC1=0.841	
RR for C2-1=1.59	TfC2=0.2267		TfC2 =0.1367		TfC2=0.2330		TfC2=0.159	
RR for C2 =2.80			TfB1 =0.0011					
			TfB2 =0.0045					
			TfB2-1=0.0022					
			TfD1 =0.0011					

Differences between women with previous abortion and controls were high significant. $\chi^2 = 7.47$, df=1, $0.01 > p > 0.001$

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