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## Atypical ( $E_1^a$ ) and Fluoride-Resistant ( $E_1^f$ ) Cholinesterase Genes: Absent in a Native American Indian Population

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*Key Words.* Plasma cholinesterase · Genetic variants · American Indians · Population study

*Abstract.* A population of 358 Navajo Indian children screened for serum cholinesterase variants failed to show the presence of either atypical or fluoride-resistant genes. This is the first significant anthropological observation of the absence of both variants in a native North American population.

Identification of individuals who demonstrate abnormal resistance and hypersensitivity to the muscle relaxant succinylcholine (succinylcholine) has led to discovery of a number of genetic variants of serum cholinesterase (Enzyme Commission designation, acylcholine acyl-hydrolase EC 3.1.1.8). Because of pharmacogenetic interrelationships and increased interest in human genetic polymorphism, the frequency of serum cholinesterase mutants has been determined in many populations for alleles of the  $E_1$  locus, as well as, the  $E_2$  locus [1-6]. Alleles of the  $E_1$  locus control synthesis of serum cholinesterase variants and can be identified using selective inhibitors in the enzymatic assay, e. g., dibucaine and sodium fluoride [7, 8]. It is generally agreed that at least four alleles exist at the  $E_1$  locus:  $E_1^u$  for usual or normal esterase;  $E_1^a$  for atypical esterase;  $E_1^f$  for fluoride-resistant type and  $E_1^s$  for the silent gene [9]. A new allele at the  $E_1$  locus has recently been reported and termed  $E_1^j$  [10, 11]. The  $E_1^j$  allele results in a 65-70% reduction in the number of circulating enzyme molecules and can be identified only when combined in the genotypic form  $E_1^aE_1^j$  or  $E_1^fE_1^j$ . Altogether, these five alleles account for 15 different genotypes which can be identified by biochemical and/or pedigree studies. The  $C_5^+$  variant of serum cholinesterase is controlled by the  $E_2$  locus and can be identified only by electrophoretic techniques [12].

In the spring of 1974, venous blood samples were obtained from 358 Navajo children enrolled in the Toyei Boarding School, an elementary school for Navajo children located in Steamboat, Arizona. Children ranged in age from 6 through 15 years and all lived at the school, although approximately one third returned to their Reservation home on any given weekend. Serum cholinesterase genotypes were determined using sodium fluoride as a selective inhibitor in 0.05 molar Tris and phosphate buffers, pH 7.4, using 2.0 millimolar butyrylthiocholine iodine as substrate [13,14]. We did not examine specimens for the  $C_5^+$  variant.

All children examined were found to be homozygous for the usual form of the enzyme except for one child who was identified as heterozygous atypical ( $E_1^u E_1^a$ ). This child was excluded from final data analysis because his father was known not to be Navajo.

The complete absence of both atypical and fluoride-resistant genes in this native North American Indian population is similar to that in native South American populations where 491 individuals belonging to two Venezuelan and Bolivian tribes failed to demonstrate either the atypical or fluoride-resistant gene [15]. However, LISKER *et al.* [16] found a frequency of 0.005 for the atypical gene,  $E_1^a$ , in 13 tribes of Mexican Indians. In an earlier report LISKER *et al.* [17] found a frequency of 0.009 for the atypical gene,  $E_1^a$ , in 377 Mexican Indians who belonged to 4 different linguistic groups. The latter report stated that the individuals examined were apparently 'pure' Indians, but blood group studies showed the existence of a small degree of admixture with Caucasians. Frequency of the fluoride-resistant gene was not determined in studies reported by LISKER *et al.* [16, 17]. TASHIAN *et al.* [18] screened a population of Xavante Indians of the Brazilian Mato Grosso and encountered no serum cholinesterase variants. These findings suggest that both atypical and fluoride-resistant genes were either absent or had an extremely low frequency among ancestors of present day Amerindians. In an earlier study we noted the absence of atypical gene among 111 White Mountain Apache children while ascertaining frequencies of serum cholinesterase  $E_1^a$  and  $E_1^f$  alleles in a cross-sectional representation of US Caucasian children to be 0.0177 and 0.0066, respectively [13, 14]. The frequency of atypical and fluoride-resistant alleles in US Caucasian children is similar to reported frequencies for these two variants found in European countries [6].

Our finding has practical significance and should be of interest to population geneticists and anthropologists. Prolonged apnea due to suxamethonium sensitivity often occurs in individuals heterozygous and homozygous for the atypical and fluoride-resistant variants ( $E_1^a E_1^f$ ;  $E_1^a E_1^a$ ;  $E_1^f E_1^f$ ). The chance of this happening among Navajo Indians should be extremely rare. The data

also indicate that the gene pool of this native North American Indian population, like that of South American Indians, has remained relatively stable with little admixture with those races, primarily Caucasian, demonstrating atypical and fluoride-resistant genes.

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