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Proposed Nomenclature for Human Butyrylcholinesterase Genetic Variants Identified by DNA Sequencing

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SUMMARY

1. New information identifying nucleotide alterations of human butyrylcholinesterase allows the use of more specific nomenclature for the variants commonly known as atypical, fluoride, silent, and K variant.

2. In addition to suggesting a system of trivial names and abbreviations, we provide a list of formal names that follow the guidelines of the Committee for Human Gene Nomenclature.

3. It is suggested that formal names be included in publications whenever possible.

INTRODUCTION

There is a need for a systematic nomenclature that reflects new knowledge of the structure of human butyrylcholinesterase (BCHE, gene; BChE, protein). Specific nucleotide and amino acid alterations in certain genetic variants have recently been identified (McGuire *et al.*, 1989; Nogueira *et al.*, 1990). Our proposal for a new nomenclature recognizes the need to relate the names contained in over 30

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years of literature to the new information. Therefore, we propose to use a set of trivial names and trivial abbreviations that reflect the old established names, and in addition, we provide a list of formal names that follow the guidelines of the Committee for Human Gene Nomenclature (Shows *et al.*, 1987; P. J. McAlpine, personal communication).

RECOGNIZED GENETIC VARIANTS

Nine genetic variants of human serum butyrylcholinesterase are listed in Table I. In most cases variants were recognized after patients responded abnormally to the muscle relaxant succinylcholine. For example, a person who is homozygous for the atypical form of serum butytylcholinesterase experiences 30 min to 2 hr of muscle paralysis rather than the intended 2 to 3 min after receiving a single dose of succinylcholine (Kalow, 1962; Viby-Mogensen, 1983). Variants with increased activity are resistant to succinylcholine and may require two to three doses to achieve the desired state of paralysis. To date succinylcholine is the only drug known to cause abnormal clinical effects in people with rare butyrylcholinesterase genetic variants. Two other drugs in the testing stages, bambuterol, a prodrug for the bronchodilator drug terbutaline used to treat asthma (Tunek and Svensson, 1988), and mivacurium chloride, a new muscle relaxant (Savarese *et al.*, 1988), also seem to have variable effects that correlate with BCHE genotype. Aspirin, cocaine, and heroin (Lockridge, 1990) are hydrolyzed by butyrylcholinesterase, but clinical studies have not been carried out to determine whether abnormal responses to these drugs correlate with a rare

Table I. Genetic Variants of Human Serum Butyrylcholinesterase

Common name	Frequency of homozygote phenotype	Reference
Normal activity		
Usual	96:100	Whittaker (1986)
Reduced activity		
Atypical	1:3500	Kalow and Staron (1957) Kalow and Gunn (1959)
Silent	1:100,000	Liddell *et al.* (1962)
Fluoride	1:150,000	Harris and Whittaker (1961)
Quantitative Variant J	1:150,000	Garry *et al.* (1976) Evans and Wardell (1984)
Quantitative Variant K	1:100	Rubinstein *et al.* (1978) Whittaker and Britten (1988)
Quantitative Variant H	2 families	Whittaker and Britten (1987)
Newfoundland	1 family	Simpson and Elliott (1981)
Increased activity		
Cynthiana Variant	4 families	Neitlich (1966) Yoshida and Motulsky (1969) Delbruck and Henkel (1979)
Johannesburg	1 family	Krause *et al.* (1988)

BCHE genetic variant. Whittaker (1986) has reviewed the biochemical properties of the rare variants. Table I does not include the C5 variant formerly attributed to a second BCHE locus because this second locus codes for a noncholinesterase protein (Masson *et al.*, 1990). The C5 variant is not important to the anesthetist.

PHENOTYPING

In our laboratory butyrylcholinesterase activity is usually measured by the method of Kalow and Lindsay (1955) using benzoylcholine as substrate. Dibucaine number is percentage inhibition of activity in the presence of 10 μM dibucaine (Kalow and Genest, 1957). Fluoride number is percentage inhibition of activity in the presence of 50 μM sodium fluoride (Harris and Whittaker, 1961). RO2 number is percentage inhibition after incubation of the plasma or serum in 10^{-8} M RO2-0683 for 1 hr prior to the addition of substrate (Evans and Wardell, 1984). RO2-0683 is the dimethylcarbamate of (2-hydroxy-5-phenylbenzyl)-trimethyl ammonium.

The phenotyping method introduced by Kalow and Genest (1957), based on dibucaine number, is an excellent and reliable method for determining whether a person has atypical cholinesterase. The atypical allele can be detected in homozygotes as well as in heterozygotes. This is a very special feature of atypical BChE, since most of the other variants cannot be identified when they occur in combination with the usual allele. It is therefore difficult or impossible to tell by phenotyping tests whether a person is a carrier of the silent, fluoride, H, J, K, or Newfoundland variant unless the family also has the atypical variant and enough members of a family are tested to determine the pattern of inheritance.

GENOTYPING

The new methods of gene amplification by the polymerase chain reaction (PCR) followed by DNA sequencing (McGuire *et al.*, 1989; Nogueira *et al.*, 1990) and PCR followed by probing with a biotinylated oligonucleotide (La Du *et al.*,

Table II. Nomenclature for Homozygous Forms of Human Butyrylcholinesterase Variants[a]

Common name	Phenotypic description	Amino acid alteration	DNA alteration	Formal name for genotype
Usual	Normal	None	None	*BCHE*
Atypical	Dibucaine resistant	70 Asp→Gly	nt 209 (GAT to GGT)	*BCHE*70G*
Silent-1	Silent, no activity	117 Gly→Frameshift	nt 351 (GGT to GGAG)	*BCHE*FS117*
Fluoride-1	Fluoride resistant	243 Thr→Met	nt 728 (ACG to ATG)	*BCHE*243M*
Fluoride-2	Fluoride resistant	390 Gly→Val	nt 1169 (GGT to GTT)	*BCHE*390V*
K variant	K polymorphism	539 Ala→Thr	nt 1615 (GCA to ACA)	*BCHE*539T*

[a] Amino acid 1 as well as codon 1 is the N terminal of the mature protein.

Table III. Nomenclature for Heterozygous Forms of Human Butyrylcholinesterase Variants[a]

Phenotype	New abbreviation	Amino acids affected		Formal name for Genotype
		Chain one	Chain two	
Usual	UU	Normal	Normal	*BCHE*
Usual	KK	539 Ala→Thr	539 Ala→Thr	*BCHE*539T/BCHE*539T*
Usual	UK	Normal	539 Ala→Thr	*BCHE/BCHE*539T*
Usual	US	Normal	117 Gly→frameshift	*BCHE/BCHE*FS117*
Usual	UF	Normal	390 Gly→Val	*BCHE/BCHE*390V*
Usual	UF	Normal	243 Thr→Met	*BCHE/BCHE*243M*
Atypical	AK/AK	70 Asp→Gly and 539 Ala→Thr	70 Asp→Gly and 539 Ala→Thr	*BCHE*70G539T/BCHE*70G539T*
Atypical	A/AK	70 Asp→Gly	70 Asp→Gly and 539 Ala→Thr	*BCHE*70G/BCHE*70G539T*
Atypical	AK/S	70 Asp→Gly and 539 Ala→Thr	117 Gly→Frameshift	*BCHE*70G539T/BCHE*FS117*
AK	AK/K	70 Asp→Gly and 539 Ala→Thr	539 Ala→Thr	*BCHE*70G539T/BCHE*539T*
AK	AU	70 Asp→Gly	Normal	*BCHE*70G/BCHE*
AU	AK/U	70 Asp→Gly and 539 Ala→Thr	Normal	*BCHE*70G539T/BCHE*
AF	AK/F	70 Asp→Gly and 539 Ala→Thr	390 Gly→Val	*BCHE*70G539T/BCHE*390V*
AF	AK/F	70 Asp→Gly and 539 Ala→Thr	243 Thr→Met	*BCHE*70G539T/BCHE*243M*
Silent	SS	117 Gly→frameshift	117 Gly→frameshift	*BCHE*FS117/BCHE*FS117*

[a] Only variants that have been sequenced to date are given, though other variants exist. Phenotype was assigned on the basis of dibucaine, fluoride, and RO2 numbers as given on pp. 93 and 94 of Whittaker (1986). Amino acid alterations were identified by DNA sequencing. The new abbreviations combine the established nomenclature (usual, atypical, fluoride, silent, K variant) with the new observation that more than 90% of all atypicals carry two mutations on the same DNA strand. We propose to use no abbreviations for the rarest variants, for example, Johannesburg and Cynthiana, but to refer to these by their full geographic location names.

1990) have allowed identification of the nucleotide alterations in the variants of BCHE. DNA sequencing overcomes the limitations of phenotyping, because all variants can be precisely identified. Furthermore the new methods discriminate among similar phenotypes, such as fluoride-1 and fluoride-2. Tables II and III list the variants identified in our laboratory by DNA sequencing. Figures showing the location of nucleotide and amino acid substitutions within the complete sequence of human BChE have been published (Arpagaus *et al.*, 1990; Lockridge, 1990). A limitation of DNA sequencing is that it is slow compared to phenotyping, requiring 1 week rather than 30 min to analyze one person.

ATYPICAL

All atypicals sequenced to date have a substitution at nucleotide 209, changing A to G and changing codon 70 from aspartic acid to glycine (McGuire *et al.*, 1989). The number of unrelated atypical alleles we have sequenced is 20. Atypical BChE has the kinetic properties of an enzyme that has a deficient anionic site. Atypical BChE has a reduced affinity for neutral substrates and a normal turnover number, k_{cat} (Lockridge and La Du 1978). Therefore, Asp 70 appears to be an essential component of the anionic site.

A second substitution was found in greater than 90% of atypical genes. The second substitution was at nucleotide 1615, where G was replaced by A and codon 539 was changed from alanine to threonine. Since some atypicals lack this second substitution we conclude that the atypical phenotype is due to the substitution of Asp 70 by Gly (McGuire *et al.*, 1989). The 539 Ala→Thr mutation represents the K variant. Thus, a single BCHE chromosomal strand may carry two mutations: the mutation responsible for the atypical phenotype and a mutation responsible for the K variant phenotype. This linkage disequilibrium would be expected if a founder were responsible for the atypical genes, and his atypical mutation occurred on a chromosomal strand carrying the K mutation. The disequilibrium with the K variant mutation may well explain why there are about one-third less atypical than usual BChE molecules per ml of serum (Eckerson *et al.*, 1983).

K VARIANT

The K variant, named in honor of Werner Kalow, is associated with a 33% reduction in serum BChE activity (Rubinstein *et al.*, 1978). By sequencing the DNA of family members and by pedigree analysis, we found that the K phenotype was associated with a single nucleotide substitution at nucleotide 1615, which changed codon 539 from alanine to threonine (Bartels *et al.*, 1989). Our conclusion that this substitution explained the K variant was supported by the observation that the frequency of the 539 Ala→Thr mutation was equivalent to the 1% frequency of the homozygote K variant (Evans and Wardell, 1984; Whittaker and Britten, 1985). Though the K variant is the most common

mutation of BChE, its clinical importance has been noted only when it is present in association with atypical BChE.

FLUORIDE

The fluoride phenotype is resistant to the inhibitor NaF. Two mutations causing the fluoride phenotype have been found so far. One family had a substitution at nucleotide 728 of C to G, changing codon 243 from Thr to Met, while three families had a substitution at nucleotide 1169 of G to T, changing codon 390 from Gly to Val. The first fluoride mutation identified by DNA sequencing is fluoride-1, the second is fluoride-2, etc.

SILENT

The silent phenotype is characterized by zero BChE activity or very low activity, less than 2% of normal (Rubinstein *et al.*, 1970). We have identified one type of silent mutation called silent-1 or silent-Ann Arbor (Nogueira *et al.*, 1990). The mutation in Table II was found in two unrelated families, one Italian-American and one Persian. This is a complex mutation in which the T at nucleotide 351 was replaced by two nucleotides, AG. The frameshift caused a stop codon to appear at codon 129 so that protein synthesis was prematurely terminated. Only a truncated BChE, about 22% of the length of the usual enzyme, could be produced. It lacked the active site serine at position 198 and therefore had no activity. The serum from this silent phenotype did not cross-react with antibody to human serum BChE and had zero activity with benzoylcholine and alpha-naphthylacetate. Another serum with the silent phenotype also had zero BChE activity and no cross-reactive material but did not contain the above mutation. Therefore a silent-2 is likely to exist.

NOMENCLATURE

Trivial Names A modification of the trivial names for the genetic variants has already been suggested above. A number following the trivial name, for example, fluoride-1, fluoride-2, can be used to indicate that the fluoride phenotype includes several different nucleotide alterations (Table II). Following a practice established for the hemoglobin variants, a geographic name can be used as a trivial name. The geographic name can be appended to an already existing trivial name, as in silent-Ann Arbor, or can be used alone as in variants Newfoundland, Cynthiana, and Johannesburg.

In daily laboratory work it is our practice to use the simplest names possible. A system of two-letter abbreviations is well established but fails to describe the fact that most atypicals contain two mutations. Therefore, we propose a system of two-, three-, and four-letter abbreviations in Table III. A two-letter abbreviation

is used for a genotype having one mutation per DNA strand, for example, SS for homozygous silent. Three- and four-letter abbreviations are used when one or both alleles contain a double mutation. The double mutation on a single DNA strand of atypicals is represented by two letters, AK. If only one strand has a double mutation while the second strand has a single mutation, the abbreviation contains three letters, for example, AK/K. The genotype abbreviation for a double mutation on both alleles is AK/AK with a slash separating the two alleles. This system of trivial abbreviations does not distinguish between fluoride-1 and fluoride-2, both being refferred to as F, but numbers could be added if this distinction becomes necessary.

Formal Names. The Human Gene Mapping Nomenclature Committee has designated *BCHE* as the gene symbol for butyrylcholinesterase (P. J. McAlpine, personal communication). *BCHE* now replaces *CHE1,* the former symbol. *BCHEL1* and *BCHEL2* are the butyrylcholinesterase-like sites to which the cDNA probe hybridizes (Soreq *et al.,* 1987; Zakut *et al.,* 1989). Italics represent genotype, while standard type represents phenotype. An asterisk separates the symbols for gene and allele, and the single-letter amino acid symbol is used to identify mutations (Shows *et al.,* 1987). In the example *BCHE*70G,* the 70th amino acid from the N terminal of the mature protein has a substitution of glycine for aspartate (70 Asp→Gly). A slash separates alleles and indicates chromosome homologues. Frameshift is indicated by FS. In the example *BCHE*70G539T/BCHE*F117,* one allele has a double mutation (70 Asp→Gly and 539 Ala→Thr), while the second allele has a frameshift mutation at codon 117. See Table III.

The gene symbol for human acetylcholinesterase has been designated *ACHE. Drosophila,* nematode, and mouse geneticists use *Ace* as the symbol for the ACHE gene. However, Ace cannot be used for human acetylcholinesterase because all letters are not capitalized. *ACE* is not available as a gene symbol for human acetylcholinesterase because it has been assigned to a different human gene.

The gene symbol for the C5 phenotype will remain CHE2 until the C5 phenotype is better understood (P. J. McAlpine, personal communication).

ONE FUNCTIONAL BUTYRLCHOLINESTERASE GENE

There is general agreement that the rare genetic variants, atypical, fluoride, and silent, are allelic with the usual form of BChE. Linkage analysis showed that BChE was closely linked to human transferrin (Robson *et al.,* 1966; Sparkes *et al.,* 1984). When Yang *et al.,* (1984) mapped transferrin to human chromosome 3 in the long arm q21–25, it was clear that BCHE also mapped in this region. The *in situ* hybridization studies of Soreq *et al.,* (1987) with a human BCHE cDNA probe confirmed that chromosome 3q21–26 was the location of a human BCHE gene.

The idea that two loci may code for human BChE originated in the work of Harris *et al.,* (1963), who reported that an extra, slow-migrating component, C5,

was inherited independently of the atypical variant. It was unclear whether C5 represented a second BCHE gene or represented a noncholinesterase protein. It became common to refer to two BCHE loci and to lose sight of the possibility that the second locus could be coding for a modifying protein that was not BChE, although Scott and Powers (1974) concluded that C5 was a hybrid between BChE and a second protein, whose identity was unknown. The chromosomal location of C5, whose gene symbol is CHE2, was tentatively identified by Lovrien *et al.* (1978) as chromosome 16 based on a weak linkage with Hp and a lod score of 2.3. Marazita *et al.* (1989) also showed a weak linkage of CHE2 and haptoglobin on chromosome 16, with a lod score of 2.5. A lod score less than 3.0 is considered statistically insignificant and therefore both Lovrien *et al.* (1978) and Marazita *et al.* (1989) were cautious in assigning CHE2 to chromosome 16. A much stronger lod score of 4.2 was obtained by Eiberg *et al.* (1989) for the linkage between γ-crystallin gene cluster, CRYG, and CHE2, thus mapping CHE2 to chromosome 2 bands q33–q35. Eiberg's result that CHE2 mapped to chromosome 2 did not, by itself, rule out the possibility that CHE2 represented a second BCHE locus. This interpretation can, however, be made from the data of Soreq *et al.* (1987) and Zakut *et al.* (1989), who showed no hybridization of BCHE cDNA to chromosome 2.

Additional evidence supporting the interpretation that the BChE component of C5 originates from the same BCHE locus as the major BChE enzyme comes from the work of Arpagaus *et al.* (1990) and Masson *et al.* (1990). Arpagaus *et al.* (1990) isolated the BCHE gene and reported that the human genome contains a single copy of the BCHE gene. This conclusion can be challenged with the argument that Arpagaus *et al.* examined DNA from three individuals and would therefore have missed a second BCHE gene that existed in only a small percentage of the population. Masson *et al.* (1990) examined the possibility that a small percentage of the population might carry two BCHE genes. The most likely section of the population that might carry a second gene was the group that carried the C5 component, a group that includes 10% of Caucasians (Robson and Harris, 1966). Therefore, Masson *et al.* (1990) prepared Southern blots from total genomic DNA isolated from three people with the C5 phenotype. Hybridization results revealed that people with the C5 phenotype had a single copy of the BCHE gene and that this BCHE gene was indistinguishable from the BCHE gene that is present in people lacking C5. The argument that can be raised against this conclusion is that hybridization conditions were too stringent to detect a second BCHE locus that might be less than 70% identical with the major BCHE locus.

The interpretation we favor is that C5 is a hybrid protein encoded by the BCHE gene on chromosome 3 bands q21–q26 and an unidentified gene on chromosome 2. A recent example of the ability of serum BChE to combine with a foreign protein comes from the work of Masson (1989), who found that the electrophoretic band termed C2 is a disulfide-linked complex between one BChE subunit and one albumin molecule. An alternative interpretation for C5 was presented by Soreq *et al.* (1987), who suggested that CHE2 codes for a protein which is similar to that encoded by the BCHE locus and that CHE2 maps to chromosome 16.

The question of the number of BCHE genes is very important to the Human Genome Mapping and Sequencing project. Single-copy DNA sequences (that occur only once in the genome) that can be easily recovered by PCR are proposed as the landmarks that define position on the physical map (Olson *et al.*, 1989). In our view BCHE can be one of these sequence-tagged sites (STS) for the long arm of chromosome 3. To date we have recovered BCHE sequences by PCR from total genomic DNA of approximately 100 individuals with results that are completely consistent with the existence of a single functional BCHE gene. Though BCHE cDNA hybridized to two regions on chromosome 3 (Zakut *et al.*, 1989) and one region on chromosome 16 (Soreq *et al.*, 1987; Zakut *et al.*, 1989), these additional regions do not interfere with amplification of the BCHE gene by PCR.

The possibility exists that the additional loci that hybridize to BCHE cDNA (Soreq *et al.*, 1987; Zakut *et al.*, 1989) are genes homologous to the major form of BCHE. The homology might be too low to allow hybridization to PCR oligonucleotides, and too low to hybridize to cDNA on Southern blots, but high enough to be responsive to the conditions used in hybridization to chromosomes. If this is the case, then the question becomes one of definition as to what percentage homology classifies a gene as BCHE. This question was raised at the third CHE meeting, where it was concluded that sequence information from many more animals was needed before it would be clear what distinguished butyrylcholinesterase from several related esterases including acetylcholinesterase and carboxylesterases.

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