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Emerging significance of butyrylcholinesterase

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Abstract

Butyrylcholinesterase (BChE; EC 3.1.1.8), an enzyme structurally related to acetylcholinesterase, is widely distributed in the human body. It plays a role in the detoxification of chemicals such as succinylcholine, a muscle relaxant used in anesthetic practice. BChE is well-known due to variant forms of the enzyme with little or no hydrolytic activity which exist in some endogamous communities and result in prolonged apnea following the administration of succinylcholine. Its other functions include the ability to hydrolyze acetylcholine, the cholinergic neurotransmitter in the brain, when its primary hydrolytic enzyme, acetylcholinesterase, is absent. To assess its potential roles, BChE was studied in relation to insulin resistance, type 2 diabetes mellitus, cognition, hepatic disorders, cardiovascular and cerebrovascular diseases, and inflammatory conditions. Individuals who lack the enzyme activity of BChE are otherwise healthy, until they are given drugs hydrolyzed by this enzyme. Therefore, BChE is a candidate for the study of loss-of-function mutations in humans. Studying individuals with variant forms of BChE can provide insights into whether they are protected against metabolic diseases. The potential utility of the enzyme as a biomarker for Alzheimer's disease and the response to its drug treatment can also be assessed.

Key Words: Esterase; Acetylcholinesterase; Variant; Cholinergic; Metabolic syndrome; Cognition; Knockout model

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Core Tip: Butyrylcholinesterase (BChE), a hepatic enzyme, hydrolyzes the muscle relaxant succinylcholine. Individuals with variant forms of the enzyme are healthy until they are administered succinylcholine during anesthesia. The enzyme may have regulatory roles in lipid metabolism, cholinergic response, and Alzheimer's disease. People with variant forms of the enzyme are natural human knockout models and can be followed up to study the metabolic impact of harboring variant forms of BChE.

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INTRODUCTION

Butyrylcholinesterase (BChE), belonging to the esterase group of enzymes, is a part of the serine hydrolase superfamily[1, 2]. Esterases hydrolyze compounds that contain ester, amide, and thioester bonds[1]. BChE (EC 3.1.1.8) and acetylcholinesterase (AChE, EC 3.1.1.7) share a similar three-dimensional structure[3]. BChE is believed to have resulted from a duplication of an ancestral AChE gene[4]. AChE is responsible for the hydrolysis of acetylcholine at the neuromuscular junction. The roles of BChE are less well-defined: It hydrolyzes succinylcholine and bambuterol, which are used as muscle relaxants in anesthesiology[1].

EVOLUTIONARY ASPECTS AND CHEMISTRY

The *BChE* gene (HGNC: 983; MIM: 177100) exists across life forms[5] including invertebrates[6]. The concentrations of BChE exceed those of AChE in most tissues except the brain and muscle[3]. In the AChE knockout mouse model, BChE can compensate for the lack of AChE[7,8]. A convergent evolutionary mechanism is believed to have occurred between AChE and BChE[6].

BChE, which is mapped on chromosome 3 (3q26), exists in four molecular forms in plasma. The tetrameric form comprises nearly 90% of total plasma cholinesterase activity[2]. In a monomer, it consists of a common α/β hydrolase fold, flanked by α helices. The active site gorge volume of BChE is larger than that of AChE[9] and is shaped like a bowl [2]. AChE, though, has nearly 40% more aromatic residues. The active gorge consists of an acylation site for catalysis and pockets for choline-binding. It is rimmed by a peripheral anionic site. The catalytic activity of BChE depends on H-bond stabilization. In simulation studies, inhibitors were shown to reach the catalytic cavity due to the flexible entrance of the gorge[10].

TISSUE DISTRIBUTION

BChE is found in the lungs, plasma, brain, and heart. The highest levels of *BChE* mRNA are found in the liver, followed by the lung and the brain[4], where it is present at neuromuscular junctions. BChE is also expressed in brain astrocytes. The close association of neurons and glia has been termed the 'tripartite synapse', whereby glia exchange information with neurons[11].

BIOLOGICAL ROLES OF BUTYRYLCHOLINESTERASE

The role of BuChE in anaesthetic practice is well-recognized as a degrading enzyme of neuromuscular blockers succinylcholine and mivacurium[12]. Mutant forms of the enzyme have low or absent activity, resulting in prolonged apnea with the use of these muscle relaxants.

BChE levels are low in systemic conditions like liver disease, renal disease, malnutrition, malignancies, and burns[13].

It participates in the first-phase detoxification reaction against natural and exogenous toxins[14] (Table 1).

In the brain, BChE is present in the glial cells near the hippocampus and amygdala[15]. It may interact with ghrelin in the brain; in mice, increased expression of BChE is associated with low blood levels of ghrelin and reduced aggressive behavior[16].

ASSOCIATION OF BUTYRYLCHOLINESTERASE AND ENVIRONMENTAL TOXINS

BChE activity is principally found in 'tissues of first contact', such as the lungs, liver, skin, and blood. It plays a role in the activation of pro-drugs as well as in metabolizing drugs to inactive forms[17]. The biotransformation ability changes due

Table 1 Potential roles of butyrylcholinesterase

Known functions	Metabolism of drugs and toxins (<i>e.g.</i> , succinylcholine, carbamates, glucoalkaloids)	
	Affected by dietary fats	
	Influences the expression of metabolic syndrome, <i>via</i> action on lipids	
Associations and predictors of outcomes in disease states	Nutritional status	
	Hepatic disorders	
	Cardiovascular disease	Acute coronary syndrome
		Acute myocardial infarction
	Injuries to brain and cerebrovascular and disease	Ischemic brain stroke
		Traumatic brain injury
		Predisposition
	Alzheimer's disease	Onset
		Response to anticholinesterase medications
	Pre-eclampsia	
	Inflammatory and infections	Sepsis
		HIV infection
		Hansen's disease
	Other conditions	Wilson's disease
		Chronic obstructive pulmonary disease

HIV: Human immunodeficiency virus.

to alterations in the macromolecular structure of the enzyme[17].

Other potential toxins that are inactivated by BChE include carbamates and plants containing glucoalkaloids[18,19].

To derive reference ranges of AChE and BChE, their levels were measured in 387 young and healthy individuals (201 men and 186 women aged between 18 and 45 years)[18], which is useful for comparison in pathological states[20].

Gene polymorphisms of *BChE* were studied in relation to groundwater fluoride toxicity[21]. In clinically healthy adults from Pakistan, fluorosis was associated with elevated BChE activity[21].

BUTYRYLCHOLINESTERASE, METABOLIC SYNDROME, AND DIABETES MELLITUS

BChE activity in rats was influenced by dietary fat[22], perhaps due to increased release from hepatocytes[23]. Among subjects with type 2 diabetes from southern India, the plasma levels of BChE were inversely related to serum cholesterol ($P < 0.05$)[24]. The enzyme may not directly cause metabolic syndrome but may serve as a marker for this condition[25].

Similar associations were reported between BChE activity and weight in children[26]. Plasma BChE was proposed as a marker of chronic low-grade inflammation[27]. In Japanese subjects (171 with type 2 diabetes and 88 controls), serum BChE correlated with adiposity, serum lipids, and HOMA-R[28]. To assess the risk of mortality with the levels of BChE, 813 subjects were followed up from 1985-1987 to 1996. Those in the lowest quintile of BChE activity had higher mortality[29]. Body mass index mediates changes in BChE activity in healthy young men and women (age: 18-25 years)[30].

There are other interesting observations. Extracts from the fruit *melanocarpa* affected BChE activity[31]. Elevated BChE levels predicted the development of type 2 diabetes[32] and its vascular complication[33]. Increased levels of BChE may be associated with lower AChE levels, which play an anti-inflammatory role[34]. Exposure to BChE protects cultured pancreatic cells by reduced formation of toxic amylin oligomer[35].

BUTYRYLCHOLINESTERASE AND COGNITION

Alzheimer's disease (AD) that often accompanies aging is the most common cause of cognitive decline[36]. According to the cholinergic hypothesis, degeneration of cholinergic neurons in the basal forebrain results in cognitive dysfunction in

AD[37]. Other conditions that occur *via* the cholinergic system include amyloid deposition, tau phosphorylation, neuroinflammation, and vascular damage (Pozzi *et al*[38], 2022). Acetylcholine, the neurochemical transmitter in the cholinergic synapses, is inactivated by AChE, and to a lesser extent by BuChE. The cholinergic system is part of the cholinergic anti-inflammatory pathway. The cholinergic hypothesis received additional support by the finding that cholinesterase inhibitor drugs which increase acetylcholinesterase at the synaptic cleft are effective in the management of AD[39].

Apart from its role in the cholinergic hypothesis, BuChE has been implicated in the deposition of amyloid. Amyloid hypothesis proposes that abnormal folding of β -amyloid protein may contribute to the pathogenesis of AD[40]. A variant form of the enzyme, called K-variant (Ala567Thr (A539T)), may act synergistically with others such as the $\epsilon 4$ allele of apolipoprotein E and iron as a risk factor for AD[41,42].

BUTYRYLCHOLINESTERASE IN RELATION TO OTHER CONDITIONS

Liver disorders and malnutrition

BChE measurement is sometimes included in the panel of liver function tests due to its hepatic origin. It is an indicator of acute hepatitis or cirrhosis of the liver[14].

BChE levels are altered by inflammatory processes: They are low in acute inflammation and normalize once inflammation resolves[43]. BChE levels were low in malnourished children and in subjects with visceral undernutrition[44,45]. It can be used as a marker of nutritional status among the elderly[46].

Coronary artery disease

Acute coronary syndrome encompasses a range of conditions from angina pectoris to irreversible damage of the myocardium. BChE levels could differentiate healthy subjects from those with acute myocardial infarction (AMI). BChE activity was lower in acute myocardial infarction (AMI) ($n = 85$) compared with controls ($n = 45$) ($P < 0.001$)[47,48]. Similar observations were reported by Sulzgruber *et al*[49] in 2015. Higher BChE levels were associated with greater mortality-free survival in acute coronary syndrome. The strongest effect was observed among people aged 45-65 years. Similar findings of mortality were reported in subjects undergoing veno-arterial extracorporeal membrane oxygenation treatment after cardiac surgery[50].

Disorders of the brain

In ischemic brain stroke, BChE levels were measured in 33 subjects with acute ischemic stroke within 12 h of onset and in 29 controls. Stroke subjects had lower BChE activity compared to controls[51].

Among 188 patients with traumatic brain injury within 72 h of injury, non-survivors ($n = 42$; 22.3%) had lower levels of BChE activity[52]; they had an acute decrease of enzyme activity.

Pre-eclampsia

Pre-eclampsia, which occurs in pregnancy, is characterized by hypertension, proteinuria, and other maternal-related dysfunctions. BChE levels were measured in 198 unrelated women having pre-eclampsia and 101 unrelated women with normal pregnancy. Pre-eclampsia was associated with lower BChE activity[53].

Sepsis

Sepsis, presenting with acute organ dysfunction, is a common cause of mortality in the intensive care setting. To identify the severity of sepsis, BChE levels were used as a biomarker. Those who died within 90 d of admission had lower levels of BChE. Admission levels of the enzyme could predict those who survived 90 d[54]. Measurement of BChE could complement other ways of predicting the outcome of patients admitted in intensive care units. Using a newer definition of sepsis, 'life-threatening organ dysfunction due to a dysregulated host response to infection', Peng *et al*[55] showed that lower levels of BChE activity are an independent risk factor for the 30-d death rate in sepsis-3 patients.

Infections

The 6-mo outcome of subjects receiving highly active antiretroviral therapy for HIV infection was assessed in relation to the levels of BChE. Low levels of BChE were seen in 25.5% (129/505) of subjects with infection. In the first year, 16.6% of patients died ($n = 84$). Low BChE levels were associated with a survival of (64.5 \pm 4.5)% at one year compared to (87.6 \pm 1.8)% in those with normal levels[56].

In Hansen's disease, genotyping of an atypical BChE allele (70G; rs1799807) and five additional single nucleotide polymorphisms (SNPs) reported higher allele (70G) and genotypic (70DG) frequencies in rs1799807. Atypical variants of the enzyme could predispose to infection[57], by interfering with the inflammatory response against the infective agent. Similarly, children with foot and mouth disease caused by enterovirus 71 infection had increased BChE levels[58].

Fertility

BChE was measured in idiopathic unexplained infertility, a day before and a day after intrauterine insemination. A positive correlation between BChE levels and total antioxidant activity on the day before the procedure was observed[59].

Other conditions

BChE was measured in untreated Wilson's disease and in chronic obstructive pulmonary disease. Pilot studies showed that along with ceruloplasmin, BChE could be used as a biomarker in Wilson's disease[60]. In chronic obstructive pulmonary disease ($n = 153$), BChE levels were elevated[61].

Studies in animals

Dogs with hypercortisolism had elevated serum BChE activity, related either to a direct effect of glucocorticoids or to changes in lipid metabolism associated with hypercortisolism[62]. Elevated salivary levels of BChE were reported in dogs with parvovirus infections[63].

The underlying pathogenic mechanism in all these disparate conditions appears to involve dysregulation of the inflammatory response leading to adverse outcome.

Cholinergic control of inflammation

Inflammation is part of a physiological response that is protective against noxious environmental factors. In a recent review, Medzhitov[64] proposed that inflammation ensures that homeostasis is maintained, and tissues retain their functional and structural integrity. It is regulated by the immune system, hormones, and neural signals.

The vagus nerve conveys information from the brain to attenuate the inflammatory process. It integrates signals from the hypothalamic-pituitary-adrenal axis and through the cholinergic anti-inflammatory pathway[65]. Bonaz *et al*[66] proposed that the anti-inflammatory properties of the vagus nerve may suggest the therapeutic implications of stimulating the nerve.

BChE may also influence the outcomes of coronavirus disease 2019 (COVID-19) *via* its effect on chronic low-grade inflammation. It could also serve as a biomarker for COVID-19 outcome; subjects with COVID-19 may be studied in subjects with variant forms of BChE[34,64].

BChE activity was predictive of 28-d mortality in critically ill COVID-19 patients[67]. A recent report indicates higher mortality in subjects with low or declining levels of serum BChE during hospitalization[68].

KNOCKOUT ANIMAL MODELS TO ELUCIDATE FUNCTION OF GENES

In functional genomics, gene knockout animal models are used to determine the function of genes. When a specific gene is inactivated, the resultant phenotype can provide information about its function[69]. Humans with loss-of-function genes give better insights than animal models[70]. The differences may relate to the other gene regulators upstream or downstream as well as environmental factors[71].

MacArthur *et al*[72] reported that a healthy person has an average of 100 inactivated genes, of which 20 are homozygous. A whole-exome sequencing study among European populations ($n = 1432$) reported that of loss-of-function mutations, nearly 45% ($n = 76$) were newly identified[73]. Narasimhan *et al*[74] studied the effects of rare gene knockouts in adults born of consanguineous marriage. Exome sequencing data in 3222 adults of Pakistani origin domiciled in Britain were linked to their lifelong health records. They did not find any relationship between those with loss-of-function genes and their consultation for health issues or prescription medication use. The latter two were taken as surrogate markers for their state of health.

Loss-of-function mutations can result from: (1) Nonsense SNPs leading to a premature stop codon, producing a truncated protein sequence; (2) splicing can be affected by an SNP at a canonical splice site; (3) an insertion or deletion variant located in the gene coding region can disrupt the full-length transcript leading to frameshifts; and (4) loss-of-function mutations can arise from the loss of an initiation codon[75].

Individuals with loss-of-function mutations who are apparently healthy were referred to as 'experiments of nature'. Studying them could help in the search for new drug targets and in identifying or exploring whether such mutated genes could have beneficial effects[76].

The nascent field of studying natural human knockouts and the genotype-phenotype correlation can provide insights into population genetics and the evolution of genes[69,71].

Butyrylcholinesterase and its variants qualify as natural human knockouts: Other than prolonged apnea following exposure to succinylcholine, individuals with variant forms of BChE are apparently healthy[77].

SIGNIFICANCE OF STUDYING BUTYRYLCHOLINESTERASE VARIANTS

Unlike other gene knockout animal models, variants of BChE have a high prevalence in isolated ethnic groups: Mainly south Indian from the Vysya community, and certain Eskimos in western Alaska[34]. Li *et al*[78] developed an animal *BChE* gene knockout model to test drug toxicity. The model had a normal phenotype unless exposed to the drug. Altered cognitive functions were associated with normal nicotinic receptor function, though the muscarinic receptor function was altered in the knockout model. Preliminary studies on the effect of (R)-bambuterol, a specific and reversible inhibitor of BChE, suggested that it may be used in the treatment of early cognitive decline[79].

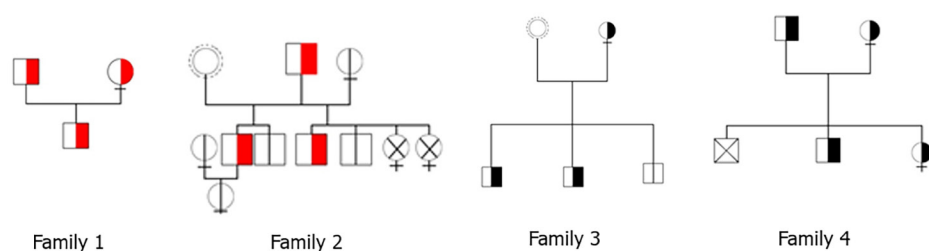


Figure 1 Phenotype of variant butyrylcholinesterase, families 1-4.

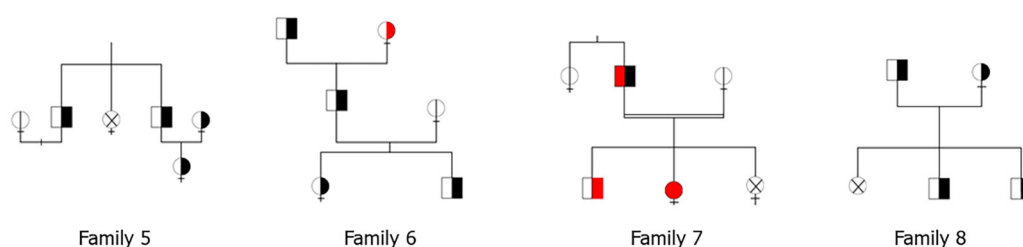


Figure 2 Phenotype of variant butyrylcholinesterase, families 5-8.

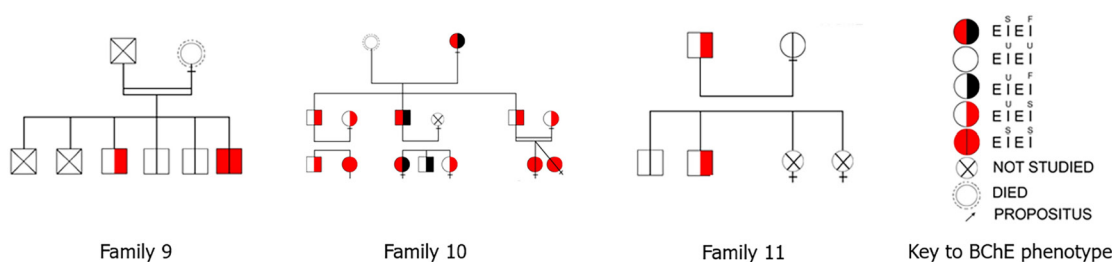


Figure 3 Phenotype of variant butyrylcholinesterase, families 9-11. BChE: Butyrylcholinesterase.

BUTYRYLCHOLINESTERASE VARIANTS IN HUMANS

Lockridge *et al* reviewed the naturally occurring genetic variants of BChE[80]. Thirty-four loss-of-function mutations were identified; all of them were tolerated, meaning that having a nonfunctional gene was compatible with life. Humans harboring silent *BChE* genes are healthy and fertile[77]. Lando *et al*[81] reported that among healthy blood donors ($n = 2609$), 59 had low plasma BChE activity.

In the Netherlands Organisation for Applied Research Prins Maurits Laboratory and Centers for Disease Control and Prevention, the frequency of BChE mutations was 9 out of 121000 alleles. Some of the mutants resulted in a complete absence of enzyme activity[80].

The commonest missense mutation, the K-variant [Ala567Thr (AS39T)], is associated with a 30% lower BChE plasma activity compared to native BChE. It is due to an unknown mutation in a regulatory region[81]. Other variants are less common except in communities such as south Indian Vysyas or Eskimos, where genotyping is not possible. Estimating dibucaine and fluoride numbers could serve as a surrogate. Family studies in the south Indian state of Andhra Pradesh showed various phenotypic forms of BChE deficiency in inbred families (oral presentation at the 12th International Meeting on Cholinesterases-Sixth International Conference on Paraoxonases at Elche (Alicante, Spain) in 2015: GR Sridhar, G Nirmala, Premlata S, Satyanarayana M. Variant butyrylcholinesterase in South India (Figures 1-4).

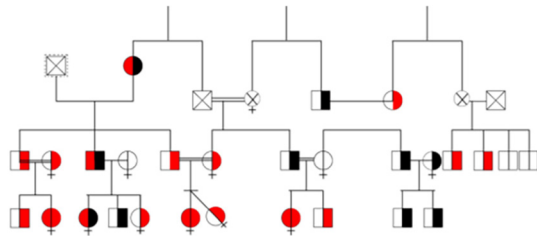
BChE activity increases with the progression of AD and may eventually replace the function of AChE[82]. Individuals with the BChE-K variant could have deleterious outcomes when donepezil is given to patients with mild cognitive impairment. It can therefore serve as a pharmacogenetic marker in the choice of drugs for cognitive impairment[82].

The reasons why non-functional proteins persisted include: (1) The active enzyme can compensate for the absent enzyme; (2) it might have acquired new beneficial functions; and (3) the enzyme may be involved in a pathway regulated by other molecules or enzyme that can substitute for it.

As mentioned earlier, succinylcholine is hydrolyzed by BChE. Administration of succinylcholine to a homozygous knockout mouse model for BChE [BChE^{-/-}] resulted in rapid death; heterozygous model [BChE^{+/-}] had less severe manifestations and recovered within 30 min[78]. AChE^{-/-} animals suffered greater toxicity to succinylcholine exposure than BChE^{-/-} mice.

Table 2 Potential areas for studies in subjects with variant forms of butyrylcholinesterase and therapeutic potential of the enzyme

Follow up of asymptomatic individuals for any protective or predictive role in cardiovascular disease and Alzheimer's disease
Production from transgenic sources as a pharmacologic agent
Potential drug target



See key in figure 3

Figure 4 Consanguinity (=) in families 7, 8, 9, and 10.

BChE is a natural drug target in which drug side effects can be minimized by knocking out its gene[83]. Knowledge from knockout models could be used to assess the effects of drugs such as donepezil in cognitive impairment.

CONCLUSION

BChE serves a critical role in the hydrolysis of esters. Unlike AChE with which it shares structural and functional properties, BChE acts on a broader number of substrates, but has lower catalytic efficiency on acetylcholine[83]. Novel ligands and mutants of BChE were developed for use in the treatment of cocaine toxicity and neurological diseases[84]. Its roles extend into cardiovascular health; recent clinical studies suggest a correlation between increased plasma BChE activity and longevity in patients with severe cardiovascular disease[16].

BChE also serves as a prognostic marker for liver and non-liver diseases, protein-energy malnutrition, and obesity by reflecting the availability of amino acidic substrates[46]. It is also involved in neurodegenerative disorders, particularly AD. BChE not only co-regulates cholinergic transmission by hydrolyzing acetylcholine alongside AChE, but potentially interferes with the course of AD. Inhibitors of BChE are therefore used in the treatment of AD and other disorders of cognition by ameliorating cholinergic deficiency[85].

Recent findings show that BChE regulates substrates such as cocaine and ghrelin. Recombinant BChE mutants and viral gene therapy are being developed against cocaine addiction, and in exploring the role of BChE in obesity[86] (Table 2).

As a therapeutic agent, phase I trials showed the safety of pure BChE, thereby giving an option in preventing nerve agent toxicity. Gene therapy using vectors that allow long-term expression of BChE after a single injection is being explored[87].

Animal studies have illustrated that pretreatment with BChE can prevent adverse effects from lethal doses of nerve agents like soman, sarin, and VX[88]. Other technologies employed to synthesise BChE include glycosylation and PEGylation that can enhance its pharmacokinetics[86].

Not all loss-of-function gene variants manifest in the same way; they may range from being mildly deleterious to neutral and sometimes, even advantageous[89]: In populations where consanguinity and Mendelian disorders are common, population-wide rapid exome sequencing may be beneficial[90,91].

BChE's multi-faceted nature, as a pharmacological target and tool, deepens our understanding of biological pathways in health and disease. Further phenotype-genotype studies will throw light on its potential effects. In this context, subjects with variant forms of BChE serve as critical comparators in such studies.

FOOTNOTES

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