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**Emerging significance of butyrylcholinesterase**

Sridhar GR *et al*. Butyrylcholinesterase

Gumpeny R Sridhar, Lakshmi Gumpeny

**Gumpeny R Sridhar,** Department of Endocrinology and Diabetes, Endocrine and Diabetes Centre, Visakhapatnam 530002, Andhra Pradesh, India

**Lakshmi Gumpeny,** Department of Internal Medicine, Gayatri Vidya Parishad Institute of Healthcare and Medical Technology, Visakhapatnam 530048, Andhra Pradesh, India

**Author contributions:** The two authors contributed equally to the writing of the manuscript.

**Corresponding author: Gumpeny R Sridhar, FRCP, Adjunct Professor,** Department of Endocrinology and Diabetes, Endocrine and Diabetes Centre, 15-12-15 Krishnanagar, Visakhapatnam 530002, Andhra Pradesh, India. sridharvizag@gmail.com

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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.

**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 mivarurium[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 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 ɛ4 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 +/- 4.5)% at one year compared to (87.6 +/- 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].

**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 Mauritis 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 homozymous 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.

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.

**REFERENCES**

1 **Fukami T**, Yokoi T. The emerging role of human esterases. *Drug Metab Pharmacokinet* 2012; **27**: 466-477 [PMID: 22813719 DOI: 10.2133/dmpk.dmpk-12-rv-042]

2 **Masson P**, Carletti E, Nachon F. Structure, activities and biomedical applications of human butyrylcholinesterase. *Protein Pept Lett* 2009; **16**: 1215-1224 [PMID: 19508180 DOI: 10.2174/092986609789071207]

3 **Li B**, Stribley JA, Ticu A, Xie W, Schopfer LM, Hammond P, Brimijoin S, Hinrichs SH, Lockridge O. Abundant tissue butyrylcholinesterase and its possible function in the acetylcholinesterase knockout mouse. *J Neurochem* 2000; **75**: 1320-1331 [PMID: 10936216 DOI: 10.1046/j.1471-4159.2000.751320.x]

4 **Johnson G**, Moore SW. Why has butyrylcholinesterase been retained? Structural and functional diversification in a duplicated gene. *Neurochem Int* 2012; **61**: 783-797 [PMID: 22750491 DOI: 10.1016/j.neuint.2012.06.016]

5 **Sridhar GR**, Lakshmi PV, Rao AA. Phylogenetic tree construction of butyrylcholinesterase sequences in life forms. *J Assoc Physicians India* 2006; **54**: 122-123 [PMID: 16715615]

6 **Pezzementi L**, Nachon F, Chatonnet A. Evolution of acetylcholinesterase and butyrylcholinesterase in the vertebrates: an atypical butyrylcholinesterase from the Medaka Oryzias latipes. *PLoS One* 2011; **6**: e17396 [PMID: 21364766 DOI: 10.1371/journal.pone.0017396]

7 **Masson P**, Lockridge O. Butyrylcholinesterase for protection from organophosphorus poisons: catalytic complexities and hysteretic behavior. *Arch Biochem Biophys* 2010; **494**: 107-120 [PMID: 20004171 DOI: 10.1016/j.abb.2009.12.005]

8 **Mesulam MM**, Guillozet A, Shaw P, Levey A, Duysen EG, Lockridge O. Acetylcholinesterase knockouts establish central cholinergic pathways and can use butyrylcholinesterase to hydrolyze acetylcholine. *Neuroscience* 2002; **110**: 627-639 [PMID: 11934471 DOI: 10.1016/s0306-4522(01)00613-3]

9 **Masson P**, Lushchekina S, Schopfer LM, Lockridge O. Effects of viscosity and osmotic stress on the reaction of human butyrylcholinesterase with cresyl saligenin phosphate, a toxicant related to aerotoxic syndrome: kinetic and molecular dynamics studies. *Biochem J* 2013; **454**: 387-399 [PMID: 23782236 DOI: 10.1042/BJ20130389]

10 **De Boer D**, Nguyen N, Mao J, Moore J, Sorin EJ. A Comprehensive Review of Cholinesterase Modeling and Simulation. *Biomolecules* 2021; **11** [PMID: 33920972 DOI: 10.3390/biom11040580]

11 **Perea G**, Navarrete M, Araque A. Tripartite synapses: astrocytes process and control synaptic information. *Trends Neurosci* 2009; **32**: 421-431 [PMID: 19615761 DOI: 10.1016/j.tins.2009.05.001]

12 **Delacour H**, Dedome E, Courcelle S, Hary B, Ceppa F. Butyrylcholinesterase deficiency. *Ann Biol Clin (Paris)* 2016; **74**: 279-285 [PMID: 27237801 DOI: 10.1684/abc.2016.1141]

13 **Andersson ML**, Møller AM, Wildgaard K. Butyrylcholinesterase deficiency and its clinical importance in anaesthesia: a systematic review. *Anaesthesia* 2019; **74**: 518-528 [PMID: 30600548 DOI: 10.1111/anae.14545]

14 **Pohanka M**. Butyrylcholinesterase as a biochemical marker. *Bratisl Lek Listy* 2013; **114**: 726-734 [PMID: 24329513 DOI: 10.4149/bll\_2013\_153]

15 **Darvesh S**, Grantham DL, Hopkins DA. Distribution of butyrylcholinesterase in the human amygdala and hippocampal formation. *J Comp Neurol* 1998; **393**: 374-390 [PMID: 9548556]

16 **Brimijoin S**, Chen VP, Pang YP, Geng L, Gao Y. Physiological roles for butyrylcholinesterase: A BChE-ghrelin axis. *Chem Biol Interact* 2016; **259**: 271-275 [PMID: 26915976 DOI: 10.1016/j.cbi.2016.02.013]

17 **Sisková K**, Bilka F, Adameová A, Balazová A, Mydla M, Pauliková I. Influence of lipid imbalance on butyrylcholinesterase activity and biotransformation efficiency. *Pharmazie* 2012; **67**: 345-350 [PMID: 22570941]

18 **Nielsen SD**, Schmidt JM, Kristiansen GH, Dalsgaard TK, Larsen LB. Liquid Chromatography Mass Spectrometry Quantification of α-solanine, α-chaconine, and Solanidine in Potato Protein Isolates. *Foods* 2020; **9** [PMID: 32252270 DOI: 10.3390/foods9040416]

19 **McGehee DS**, Krasowski MD, Fung DL, Wilson B, Gronert GA, Moss J. Cholinesterase inhibition by potato glycoalkaloids slows mivacurium metabolism. *Anesthesiology* 2000; **93**: 510-519 [PMID: 10910502 DOI: 10.1097/00000542-200008000-00031]

20 **Karasova JZ**, Maderycova Z, Tumova M, Jun D, Rehacek V, Kuca K, Misik J. Activity of cholinesterases in a young and healthy middle-European population: Relevance for toxicology, pharmacology and clinical praxis. *Toxicol Lett* 2017; **277**: 24-31 [PMID: 28465191 DOI: 10.1016/j.toxlet.2017.04.017]

21 **Bibi S**, Habib R, Shafiq S, Abbas SS, Khan S, Eqani SAMAS, Nepovimova E, Khan MS, Kuca K, Nurulain SM. Influence of the chronic groundwater fluoride consumption on cholinergic enzymes, ACHE and BCHE gene SNPs and pro-inflammatory cytokines: A study with Pakistani population groups. *Sci Total Environ* 2023; **880**: 163359 [PMID: 37030382 DOI: 10.1016/j.scitotenv.2023.163359]

22 **Van Lith HA**, Haller M, Van Tintelen G, Van Zutphen LF, Beynen AC. Plasma esterase-1 (ES-1) activity in rats is influenced by the amount and type of dietary fat, and butyryl cholinesterase activity by the type of dietary fat. *J Nutr* 1992; **122**: 2109-2120 [PMID: 1432252 DOI: 10.1093/jn/122.11.2109]

23 **Van Lith HA**, Haller M, Van Tintelen G, Lemmens AG, Van Zutphen LF, Beynen AC. Fat intake and clofibrate administration have interrelated effects on liver cholesterol concentration and serum butyryl cholinesterase activity in rats. *J Nutr* 1992; **122**: 2283-2291 [PMID: 1432266 DOI: 10.1093/jn/122.11.2283]

24 **Sridhar GR**, Nirmala G, Apparao A, Madhavi AS, Sreelatha S, Rani JS, Vijayalakshmi P. Serum butyrylcholinesterase in type 2 diabetes mellitus: a biochemical and bioinformatics approach. *Lipids Health Dis* 2005; **4**: 18 [PMID: 16150144 DOI: 10.1186/1476-511X-4-18]

25 **Han Y**, Ma Y, Liu Y, Zhao Z, Zhen S, Yang X, Xu Z, Wen D. Plasma cholinesterase is associated with Chinese adolescent overweight or obesity and metabolic syndrome prediction. *Diabetes Metab Syndr Obes* 2019; **12**: 685-702 [PMID: 31190929 DOI: 10.2147/DMSO.S201594]

26 **Rodríguez-Fuentes GA,** Arcega-Cabrera Fl, Fargher LF. Plasma and erythrocyte cholinesterase activities in children from Yucatan, Mexico: relationship with anthropometry and obesity. *Asian J Pharm Clin Res* 2015; **8:** 224-228 [DOI: 10.1016/j.scitotenv.2015.10.152]

27 **Rao AA**, Sridhar GR, Das UN. Elevated butyrylcholinesterase and acetylcholinesterase may predict the development of type 2 diabetes mellitus and Alzheimer's disease. *Med Hypotheses* 2007; **69**: 1272-1276 [PMID: 17553629 DOI: 10.1016/j.mehy.2007.03.032]

28 **Iwasaki T**, Yoneda M, Nakajima A, Terauchi Y. Serum butyrylcholinesterase is strongly associated with adiposity, the serum lipid profile and insulin resistance. *Intern Med* 2007; **46**: 1633-1639 [PMID: 17917325 DOI: 10.2169/internalmedicine.46.0049]

29 **Calderon-Margalit R**, Adler B, Abramson JH, Gofin J, Kark JD. Butyrylcholinesterase activity, cardiovascular risk factors, and mortality in middle-aged and elderly men and women in Jerusalem. *Clin Chem* 2006; **52**: 845-852 [PMID: 16527886 DOI: 10.1373/clinchem.2005.059857]

30 **Stojanov M**, Stefanović A, Džingalašević G, Mandić-Radić S, Prostran M. Butyrylcholinesterase activity in young men and women: association with cardiovascular risk factors. *Clin Biochem* 2011; **44**: 623-626 [PMID: 21402063 DOI: 10.1016/j.clinbiochem.2011.03.028]

31 **Duchnowicz P**, Ziobro A, Rapacka E, Koter-Michalak M, Bukowska B. Changes in Cholinesterase Activity in Blood of Adolescent with Metabolic Syndrome after Supplementation with Extract from Aronia melanocarpa. *Biomed Res Int* 2018; **2018**: 5670145 [PMID: 29780825 DOI: 10.1155/2018/5670145]

32 **Sato KK**, Hayashi T, Maeda I, Koh H, Harita N, Uehara S, Onishi Y, Oue K, Nakamura Y, Endo G, Kambe H, Fukuda K. Serum butyrylcholinesterase and the risk of future type 2 diabetes: the Kansai Healthcare Study. *Clin Endocrinol (Oxf)* 2014; **80**: 362-367 [PMID: 23418907 DOI: 10.1111/cen.12171]

33 **Yu R**, Ye X, Wang X, Wu Q, Jia L, Dong K, Zhu Z, Bao Y, Hou X, Jia W. Serum cholinesterase is associated with incident diabetic retinopathy: the Shanghai Nicheng cohort study. *Nutr Metab (Lond)* 2023; **20**: 26 [PMID: 37138337 DOI: 10.1186/s12986-023-00743-2]

34 **Sridhar GR.** Butyrylcholinesterase, variants and metabolic syndrome. *Adipobiology* 2018; **9:** 19-27 [DOI: 10.14748/adipo.v9.4984]

35 **Shenhar-Tsarfaty S**, Bruck T, Bennett ER, Bravman T, Aassayag EB, Waiskopf N, Rogowski O, Bornstein N, Berliner S, Soreq H. Butyrylcholinesterase interactions with amylin may protect pancreatic cells in metabolic syndrome. *J Cell Mol Med* 2011; **15**: 1747-1756 [PMID: 20807286 DOI: 10.1111/j.1582-4934.2010.01165.x]

36 **Sridhar GR**, Lakshmi G, Nagamani G. Emerging links between type 2 diabetes and Alzheimer's disease. *World J Diabetes* 2015; **6**: 744-751 [PMID: 26069723 DOI: 10.4239/wjd.v6.i5.744]

37 **Jasiecki J**, Wasąg B. Butyrylcholinesterase Protein Ends in the Pathogenesis of Alzheimer's Disease-Could BCHE Genotyping Be Helpful in Alzheimer's Therapy? *Biomolecules* 2019; **9** [PMID: 31601022 DOI: 10.3390/biom9100592]

38 **Pozzi FE**, Conti E, Appollonio I, Ferrarese C, Tremolizzo L. Predictors of response to acetylcholinesterase inhibitors in dementia: A systematic review. *Front Neurosci* 2022; **16**: 998224 [PMID: 36203811 DOI: 10.3389/fnins.2022.998224]

39 **Sridhar GR.** Acetylcholinesterase inhibitors (Galantamine, Rivastigmine, and Donepezil). In P. Riederer, G. Laux et al (eds.), NeuroPsychopharmacotherapy. *Springer Nature Switzerland AG* 20211 [DOI: 10.1007/978-3-319-56015-1\_418-1]

40 **Reid GA**, Darvesh S. Butyrylcholinesterase-knockout reduces brain deposition of fibrillar β-amyloid in an Alzheimer mouse model. *Neuroscience* 2015; **298**: 424-435 [PMID: 25931333 DOI: 10.1016/j.neuroscience.2015.04.039]

41 **Ratis RC**, Dacoregio MI, Simão-Silva DP, Mateus RP, Machado LPB, Bonini JS, da Silva WCFN. Confirmed Synergy Between the ɛ4 Allele of Apolipoprotein E and the Variant K of Butyrylcholinesterase as a Risk Factor for Alzheimer's Disease: A Systematic Review and Meta-Analysis. *J Alzheimers Dis Rep* 2023; **7**: 613-625 [PMID: 37483326 DOI: 10.3233/ADR-220084]

42 **Jasiecki J**, Targońska M, Wasąg B. The Role of Butyrylcholinesterase and Iron in the Regulation of Cholinergic Network and Cognitive Dysfunction in Alzheimer's Disease Pathogenesis. *Int J Mol Sci* 2021; **22** [PMID: 33670778 DOI: 10.3390/ijms22042033]

43 **Assis CRD**, Linhares AG, Cabrera MP, Oliveira VM, Silva KCC, Marcuschi M, Maciel Carvalho EVM, Bezerra RS, Carvalho LB Jr. Erythrocyte acetylcholinesterase as biomarker of pesticide exposure: new and forgotten insights. *Environ Sci Pollut Res Int* 2018; **25**: 18364-18376 [PMID: 29797194 DOI: 10.1007/s11356-018-2303-9]

44 **Dabke AT**, Pohowalla JN, Inamdar S, Singh SD, Mathur PS. Serum cholinesterase and histopathology of the liver in severe protein calorie malnutrition. *Indian J Pediatr* 1972; **39**: 151-157 [PMID: 4629953 DOI: 10.1007/BF02750872]

45 **Camarero González E**, Muñoz Leira V, Iglesias Guerrero M, Fernández Alvarez JA, Cabezas-Cerrato J. [Protein-energy malnutrition: its effects on 4 metabolic parameters]. *Nutr Hosp* 1995; **10**: 158-160 [PMID: 7612711]

46 **Santarpia L**, Grandone I, Contaldo F, Pasanisi F. Butyrylcholinesterase as a prognostic marker: a review of the literature. *J Cachexia Sarcopenia Muscle* 2013; **4**: 31-39 [PMID: 22956442 DOI: 10.1007/s13539-012-0083-5]

47 **Kocabaş,** Ramazan, Erenler, Ali Kemal, Yetim, Mücahit, Doğan, Tolga and Erdemli, Hacı Kemal. Butyrylcholinesterase as an additional marker in the diagnostic network of acute myocardial infarction. *Laboratoriums Medizin* 2016; **40:** 147-152 [DOI: 10.1515/Labmed-2015-0086]

48 **Nechaeva N,** Prokopkina T, Makhaeva G, Rudakova E, Boltneva N, Dishovsky C, Eremenko A, Kurochkin I. Quantitative butyrylcholinesterase activity detection by surface-enhanced Raman spectroscopy. *Sensors and Actuators B: Chemical* 2018; **259:** 75-82 [DOI: 10.1016/j.snb.2017.11.174]

49 **Sulzgruber P**, Koller L, Reiberger T, El-Hamid F, Forster S, Rothgerber DJ, Goliasch G, Wojta J, Niessner A. Butyrylcholinesterase predicts cardiac mortality in young patients with acute coronary syndrome. *PLoS One* 2015; **10**: e0123948 [PMID: 25933219 DOI: 10.1371/journal.pone.0123948]

50 **Distelmaier K**, Winter MP, Rützler K, Heinz G, Lang IM, Maurer G, Koinig H, Steinlechner B, Niessner A, Goliasch G. Serum butyrylcholinesterase predicts survival after extracorporeal membrane oxygenation after cardiovascular surgery. *Crit Care* 2014; **18**: R24 [PMID: 24479557 DOI: 10.1186/cc13711]

51 **Vaisi-Raygani A**, Tavilani H, Zahrai M, Rahimi Z, Sheikh N, Aminian M, Pourmotabbed T. Serum butyrylcholinesterase activity and phenotype associations with lipid profile in stroke patients. *Clin Biochem* 2009; **42**: 210-214 [PMID: 19028482 DOI: 10.1016/j.clinbiochem.2008.10.025]

52 **Zhang QH**, Li AM, He SL, Yao XD, Zhu J, Zhang ZW, Sheng ZY, Yao YM. Serum Total Cholinesterase Activity on Admission Is Associated with Disease Severity and Outcome in Patients with Traumatic Brain Injury. *PLoS One* 2015; **10**: e0129082 [PMID: 26107885 DOI: 10.1371/journal.pone.0129082]

53 **Rahimi Z**, Ahmadi R, Vaisi-Raygani A, Rahimi Z, Bahrehmand F, Parsian A. Butyrylcholinesterase (BChE) activity is associated with the risk of preeclampsia: influence on lipid and lipoprotein metabolism and oxidative stress. *J Matern Fetal Neonatal Med* 2013; **26**: 1590-1594 [PMID: 23650977 DOI: 10.3109/14767058.2013.795534]

54 **Zivkovic AR**, Decker SO, Zirnstein AC, Sigl A, Schmidt K, Weigand MA, Hofer S, Brenner T. A Sustained Reduction in Serum Cholinesterase Enzyme Activity Predicts Patient Outcome following Sepsis. *Mediators Inflamm* 2018; **2018**: 1942193 [PMID: 29853783 DOI: 10.1155/2018/1942193]

55 **Peng ZL**, Huang LW, Yin J, Zhang KN, Xiao K, Qing GZ. Association between early serum cholinesterase activity and 30-day mortality in sepsis-3 patients: A retrospective cohort study. *PLoS One* 2018; **13**: e0203128 [PMID: 30161257 DOI: 10.1371/journal.pone.0203128]

56 **Xu L**, Zhu B, Huang Y, Yang Z, Sun J, Xu Y, Zheng J, Kinloch S, Yin MT, Weng H, Wu N. Butyrylcholinesterase Levels on Admission Predict Severity and 12-Month Mortality in Hospitalized AIDS Patients. *Mediators Inflamm* 2018; **2018**: 5201652 [PMID: 29736152 DOI: 10.1155/2018/5201652]

57 **Gomes HJ**, Souza RL, Prevedello FC, Mira MT, Chautard-Freire-Maia EA. Investigation of Association between Susceptibility to Leprosy and SNPs inside and near the BCHE Gene of Butyrylcholinesterase. *J Trop Med* 2012; **2012**: 184819 [PMID: 22523498 DOI: 10.1155/2012/184819]

58 **Cheng BN**, Jin YL, Chen BQ, Zhu LY, Xu ZC, Shen T. Serum cholinesterase: a potential assistant biomarker for hand, foot, and mouth disease caused by enterovirus 71 infection. *Infect Dis Poverty* 2016; **5**: 27 [PMID: 27025584 DOI: 10.1186/s40249-016-0124-y]

59 **Haghnazari L**, Vaisi-Raygani A, Keshvarzi F, Ferdowsi F, Goodarzi M, Rahimi Z, Baniamerian H, Tavilani H, Vaisi-Raygani H, Vaisi-Raygani H, Pourmotabbed T. Effect of Acetylcholinesterase and Butyrylcholinesterase on Intrauterine Insemination, Contribution to Inflammations, Oxidative Stress and Antioxidant Status; A Preliminary Report. *J Reprod Infertil* 2016; **17**: 157-162 [PMID: 27478769]

60 **Hefter H**, Arslan M, Kruschel TS, Novak M, Rosenthal D, Meuth SG, Albrecht P, Hartmann CJ, Samadzadeh S. Pseudocholinesterase as a Biomarker for Untreated Wilson's Disease. *Biomolecules* 2022; **12** [PMID: 36551217 DOI: 10.3390/biom12121791]

61 **Ben Anes A**, Ben Nasr H, Garrouch A, Bennour S, Bchir S, Hachana M, Benzarti M, Tabka Z, Chahed K. Alterations in acetylcholinesterase and butyrylcholinesterase activities in chronic obstructive pulmonary disease: relationships with oxidative and inflammatory markers. *Mol Cell Biochem* 2018; **445**: 1-11 [PMID: 29234928 DOI: 10.1007/s11010-017-3246-z]

62 **Tvarijonaviciute A,** Caldin M, Martinez-Subiela S, Tecles F, Pastor J, Ceron JJ. Serum paraoxonase 1 and butyrylcholinesterase in dogs with hyperadrenocorticism. *Vet J* 2015; **203:** 262-263 [DOI: 10.1016/j.tvjl.2014.12.002]

63 **Kocatürk M**, Tecles F, Yalçın E, Cihan H, Tural M, Levent P, Cansev M, Cerón JJ, Yilmaz Z. Changes in choline and cholinesterase in saliva of dogs with parvovirus infection. *Res Vet Sci* 2021; **134**: 147-149 [PMID: 33385977 DOI: 10.1016/j.rvsc.2020.12.012]

64 **Medzhitov R**. The spectrum of inflammatory responses. *Science* 2021; **374**: 1070-1075 [PMID: 34822279 DOI: 10.1126/science.abi5200]

65 **Sridhar G,** Lakshmi G. Influence of butyrylcholinesterase on the course of COVID-19. *Biomedical Reviews* 2021; **32:** 37-46 [DOI: 10.14748/bmr.v31.7712]

66 **Bonaz B**, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. *J Physiol* 2016; **594**: 5781-5790 [PMID: 27059884 DOI: 10.1113/JP271539]

67 **Espeter F**, Künne D, Garczarek L, Kuhlmann H, Skarabis A, Zivkovic AR, Brenner T, Schmidt K. Critically Ill COVID-19 Patients Show Reduced Point of Care-Measured Butyrylcholinesterase Activity-A Prospective, Monocentric Observational Study. *Diagnostics (Basel)* 2022; **12** [PMID: 36140551 DOI: 10.3390/diagnostics12092150]

68 **Markuskova L**, Javorova Rihova Z, Fazekas T, Martinkovicova A, Havrisko M, Dingova D, Solavova M, Rabarova D, Hrabovska A. Serum butyrylcholinesterase as a marker of COVID-19 mortality: Results of the monocentric prospective observational study. *Chem Biol Interact* 2023; **381**: 110557 [PMID: 37209860 DOI: 10.1016/j.cbi.2023.110557]

69 **Borger P**. Natural Knockouts: Natural Selection Knocked Out. *Biology (Basel)* 2017; **6** [PMID: 29231847 DOI: 10.3390/biology6040043]

70 **Alkuraya FS**. Natural human knockouts and the era of genotype to phenotype. *Genome Med* 2015; **7**: 48 [PMID: 26029266 DOI: 10.1186/s13073-015-0173-z]

71 **Narasimhan VM**, Xue Y, Tyler-Smith C. Human Knockout Carriers: Dead, Diseased, Healthy, or Improved? *Trends Mol Med* 2016; **22**: 341-351 [PMID: 26988438 DOI: 10.1016/j.molmed.2016.02.006]

72 **MacArthur DG**, Balasubramanian S, Frankish A, Huang N, Morris J, Walter K, Jostins L, Habegger L, Pickrell JK, Montgomery SB, Albers CA, Zhang ZD, Conrad DF, Lunter G, Zheng H, Ayub Q, DePristo MA, Banks E, Hu M, Handsaker RE, Rosenfeld JA, Fromer M, Jin M, Mu XJ, Khurana E, Ye K, Kay M, Saunders GI, Suner MM, Hunt T, Barnes IH, Amid C, Carvalho-Silva DR, Bignell AH, Snow C, Yngvadottir B, Bumpstead S, Cooper DN, Xue Y, Romero IG; 1000 Genomes Project Consortium, Wang J, Li Y, Gibbs RA, McCarroll SA, Dermitzakis ET, Pritchard JK, Barrett JC, Harrow J, Hurles ME, Gerstein MB, Tyler-Smith C. A systematic survey of loss-of-function variants in human protein-coding genes. *Science* 2012; **335**: 823-828 [PMID: 22344438 DOI: 10.1126/science.1215040]

73 **Kaiser VB**, Svinti V, Prendergast JG, Chau YY, Campbell A, Patarcic I, Barroso I, Joshi PK, Hastie ND, Miljkovic A, Taylor MS; Generation Scotland; UK10K, Enroth S, Memari Y, Kolb-Kokocinski A, Wright AF, Gyllensten U, Durbin R, Rudan I, Campbell H, Polašek O, Johansson Å, Sauer S, Porteous DJ, Fraser RM, Drake C, Vitart V, Hayward C, Semple CA, Wilson JF. Homozygous loss-of-function variants in European cosmopolitan and isolate populations. *Hum Mol Genet* 2015; **24**: 5464-5474 [PMID: 26173456 DOI: 10.1093/hmg/ddv272]

74 **Narasimhan VM**, Hunt KA, Mason D, Baker CL, Karczewski KJ, Barnes MR, Barnett AH, Bates C, Bellary S, Bockett NA, Giorda K, Griffiths CJ, Hemingway H, Jia Z, Kelly MA, Khawaja HA, Lek M, McCarthy S, McEachan R, O'Donnell-Luria A, Paigen K, Parisinos CA, Sheridan E, Southgate L, Tee L, Thomas M, Xue Y, Schnall-Levin M, Petkov PM, Tyler-Smith C, Maher ER, Trembath RC, MacArthur DG, Wright J, Durbin R, van Heel DA. Health and population effects of rare gene knockouts in adult humans with related parents. *Science* 2016; **352**: 474-477 [PMID: 26940866 DOI: 10.1126/science.aac8624]

75 **Xu YC**, Guo YL. Less Is More, Natural Loss-of-Function Mutation Is a Strategy for Adaptation. *Plant Commun* 2020; **1**: 100103 [PMID: 33367264 DOI: 10.1016/j.xplc.2020.100103]

76 **Kaiser J**. The hunt for missing genes. *Science* 2014; **344**: 687-689 [PMID: 24833372 DOI: 10.1126/science.344.6185.687]

77 **Manoharan I**, Boopathy R, Darvesh S, Lockridge O. A medical health report on individuals with silent butyrylcholinesterase in the Vysya community of India. *Clin Chim Acta* 2007; **378**: 128-135 [PMID: 17182021 DOI: 10.1016/j.cca.2006.11.005]

78 **Li B**, Duysen EG, Carlson M, Lockridge O. The butyrylcholinesterase knockout mouse as a model for human butyrylcholinesterase deficiency. *J Pharmacol Exp Ther* 2008; **324**: 1146-1154 [PMID: 18056867 DOI: 10.1124/jpet.107.133330]

79 **Liu W**, Cao Y, Lin Y, Tan KS, Zhao H, Guo H, Tan W. Enhancement of Fear Extinction Memory and Resistance to Age-Related Cognitive Decline in Butyrylcholinesterase Knockout Mice and (R)-Bambuterol Treated Mice. *Biology (Basel)* 2021; **10** [PMID: 34062954 DOI: 10.3390/biology10050404]

80 **Lockridge O**, Norgren RB Jr, Johnson RC, Blake TA. Naturally Occurring Genetic Variants of Human Acetylcholinesterase and Butyrylcholinesterase and Their Potential Impact on the Risk of Toxicity from Cholinesterase Inhibitors. *Chem Res Toxicol* 2016; **29**: 1381-1392 [PMID: 27551784 DOI: 10.1021/acs.chemrestox.6b00228]

81 **Lando G**, Mosca A, Bonora R, Azzario F, Penco S, Marocchi A, Panteghini M, Patrosso MC. Frequency of butyrylcholinesterase gene mutations in individuals with abnormal inhibition numbers: an Italian-population study. *Pharmacogenetics* 2003; **13**: 265-270 [PMID: 12724618 DOI: 10.1097/00008571-200305000-00005]

82 **Sokolow S**, Li X, Chen L, Taylor KD, Rotter JI, Rissman RA, Aisen PS, Apostolova LG. Deleterious Effect of Butyrylcholinesterase K-Variant in Donepezil Treatment of Mild Cognitive Impairment. *J Alzheimers Dis* 2017; **56**: 229-237 [PMID: 27911294 DOI: 10.3233/JAD-160562]

83 **Ha ZY**, Mathew S, Yeong KY. Butyrylcholinesterase: A Multifaceted Pharmacological Target and Tool. *Curr Protein Pept Sci* 2020; **21**: 99-109 [PMID: 31702488 DOI: 10.2174/1389203720666191107094949]

84 **Sridhar GR.** Proteins of the Esterase Family: Patents for Some Proteins in Search of Metabolic Functions. Recent Patents on Biomarkers, 2011; **1:** 205-212. Available from: https://www.ingentaconnect.com/content/ben/rpbm/2011/00000001/00000003/art00004

85 **Geula C**, Darvesh S. Butyrylcholinesterase, cholinergic neurotransmission and the pathology of Alzheimer's disease. *Drugs Today (Barc)* 2004; **40**: 711-721 [PMID: 15510242 DOI: 10.1358/dot.2004.40.8.850473]

86 **Lockridge O**. Review of human butyrylcholinesterase structure, function, genetic variants, history of use in the clinic, and potential therapeutic uses. *Pharmacol Ther* 2015; **148**: 34-46 [PMID: 25448037 DOI: 10.1016/j.pharmthera.2014.11.011]

87 **Lockridge O,** Duysen EG, Masson P. Butyrylcholinesterase: overview, structure, and function. *Anticholinesterase Pesticides* 2011; **10:** 25-41

88 **Zhang P**, Jain P, Tsao C, Sinclair A, Sun F, Hung HC, Bai T, Wu K, Jiang S. Butyrylcholinesterase nanocapsule as a long circulating bioscavenger with reduced immune response. *J Control Release* 2016; **230**: 73-78 [PMID: 27063423 DOI: 10.1016/j.jconrel.2016.04.008]

89 **MacArthur DG,** Tyler-Smith C. Loss-of-function variants in the genomes of healthy humans. *Human Molecular Genetics* 2010; **19:** R125-R130

90 **Monies D**, Abouelhoda M, AlSayed M, Alhassnan Z, Alotaibi M, Kayyali H, Al-Owain M, Shah A, Rahbeeni Z, Al-Muhaizea MA, Alzaidan HI, Cupler E, Bohlega S, Faqeih E, Faden M, Alyounes B, Jaroudi D, Goljan E, Elbardisy H, Akilan A, Albar R, Aldhalaan H, Gulab S, Chedrawi A, Al Saud BK, Kurdi W, Makhseed N, Alqasim T, El Khashab HY, Al-Mousa H, Alhashem A, Kanaan I, Algoufi T, Alsaleem K, Basha TA, Al-Murshedi F, Khan S, Al-Kindy A, Alnemer M, Al-Hajjar S, Alyamani S, Aldhekri H, Al-Mehaidib A, Arnaout R, Dabbagh O, Shagrani M, Broering D, Tulbah M, Alqassmi A, Almugbel M, AlQuaiz M, Alsaman A, Al-Thihli K, Sulaiman RA, Al-Dekhail W, Alsaegh A, Bashiri FA, Qari A, Alhomadi S, Alkuraya H, Alsebayel M, Hamad MH, Szonyi L, Abaalkhail F, Al-Mayouf SM, Almojalli H, Alqadi KS, Elsiesy H, Shuaib TM, Seidahmed MZ, Abosoudah I, Akleh H, AlGhonaium A, Alkharfy TM, Al Mutairi F, Eyaid W, Alshanbary A, Sheikh FR, Alsohaibani FI, Alsonbul A, Al Tala S, Balkhy S, Bassiouni R, Alenizi AS, Hussein MH, Hassan S, Khalil M, Tabarki B, Alshahwan S, Oshi A, Sabr Y, Alsaadoun S, Salih MA, Mohamed S, Sultana H, Tamim A, El-Haj M, Alshahrani S, Bubshait DK, Alfadhel M, Faquih T, El-Kalioby M, Subhani S, Shah Z, Moghrabi N, Meyer BF, Alkuraya FS. The landscape of genetic diseases in Saudi Arabia based on the first 1000 diagnostic panels and exomes. *Hum Genet* 2017; **136**: 921-939 [PMID: 28600779 DOI: 10.1007/s00439-017-1821-8]

91 **Monies D**, Goljan E; Rapid Exome Consortium, Assoum M, Albreacan M, Binhumaid F, Subhani S, Boureggah A, Hashem M, Abdulwahab F, Abuyousef O, Temsah MH, Alsohime F, Kelaher J, Abouelhoda M, Meyer BF, Alkuraya FS. The clinical utility of rapid exome sequencing in a consanguineous population. *Genome Med* 2023; **15**: 44 [PMID: 37344829 DOI: 10.1186/s13073-023-01192-5]

**Footnotes**

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**Figure Legends**



**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.



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