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The C5 variant of the butyrylcholinesterase tetramer includes a noncovalently bound 60 kDa lamellipodin fragment

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Abstract

© 2017 by the authors. Licensee MDPI. Humans with the C5 genetic variant of butyrylcholinesterase (BChE) have 30–200% higher plasma BChE activity, low body weight, and shorter duration of action of the muscle relaxant succinylcholine. The C5 variant has an extra, slow-moving band of BChE activity on native polyacrylamide gel electrophoresis. This band is about 60 kDa larger than wild-type BChE. Umbilical cord BChE in 100% of newborn babies has a C5-like band. Our goal was to identify the unknown, 60 kDa protein in C5. Both wild-type and C5 BChE are under the genetic control of two independent loci, the BCHE gene on Chr 3q26.1 and the RAPH1 (lamellipodin) gene on Chr 2q33. Wild-type BChE tetramers are assembled around a 3 kDa polyproline peptide from lamellipodin. Western blot of boiled C5 and cord BChE showed a positive response with an antibody to the C-terminus of lamellipodin. The C-terminal exon of lamellipodin is about 60 kDa including an N-terminal polyproline. We propose that the unknown protein in C5 and cord BChE is encoded by the last exon of the RAPH1 gene. In 90% of the population, the 60 kDa fragment is shortened to 3 kDa during maturation to adulthood, leaving only 10% of adults with C5 BChE.

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Keywords

Butyrylcholinesterase, C5 phenotype, Lamellipodin, RAPH1, Tetramer

References

[1] Sussman, J.L.; Harel, M.; Frolow, F.; Oefner, C.; Goldman, A.; Toker, L.; Silman, I. Atomic structure of acetylcholinesterase from Torpedo Californica: A prototypic acetylcholine-binding protein. Science 1991, 253, 872–879.

[2] Dvir, H.; Harel, M.; Bon, S.; Liu, W.Q.; Vidal, M.; Garbay, C.; Sussman, J.L.; Massoulie, J.; Silman, I. The synaptic acetylcholinesterase tetramer assembles around a polyproline II helix. EMBO J. 2004, 23, 4394–4405.

[3] Nicolet, Y.; Lockridge, O.; Masson, P.; Fontecilla-Camps, J.C.; Nachon, F. Crystal structure of human butyrylcholinesterase and of its complexes with substrate and products. J. Biol. Chem. 2003, 278, 41141–41147.

[4] Li, H.; Schopfer, L.M.; Masson, P.; Lockridge, O. Lamellipodin proline rich peptides associated with native plasma butyrylcholinesterase tetramers. Biochem. J. 2008, 411, 425–432.

[5] Peng, H.; Schopfer, L.M.; Lockridge, O. Origin of polyproline-rich peptides in human butyrylcholinesterase tetramers. Chem. Biol. Interact. 2016, 259, 63–69.

[6] Larson, M.A.; Lockridge, O.; Hinrichs, S.H. Polyproline promotes tetramerization of recombinant human butyrylcholinesterase. Biochem. J. 2014, 462, 329–335.

[7] Bon, S.; Coussen, F.; Massoulie, J. Quaternary associations of acetylcholinesterase. II. The polyproline attachment domain of the collagen tail. J. Biol. Chem. 1997, 272, 3016–3021.

[8] Chitlaru, T.; Kronman, C.; Velan, B.; Shafferman, A. Overloading and removal of N-glycosylation targets on human acetylcholinesterase: Effects on glycan composition and circulatory residence time. Biochem. J. 2002, 363, 619–631.

[9] Ruiz, C.A.; Rossi, S.G.; Rotundo, R.L. Rescue and Stabilization of Acetylcholinesterase in Skeletal Muscle by N-terminal Peptides Derived from the Noncatalytic Subunits. J. Biol. Chem. 2015, 290, 20774–20781.

[10] Harris, H.; Hopkinson, D.A.; Robson, E.B.; Whittaker, M. Genetical studies on a new variant of serum cholinesterase detected by electrophoresis. Ann. Hum. Genet. 1963, 26, 359–382.

[11] Simpson, N.E. Polyacrylamide electrophoresis used for the detection of C5+ cholinesterase in Canadian caucasians, Indians, and Eskimos. Am. J. Hum. Genet. 1972, 24, 317–320.

[12] Souza, R.L.; Furtado, L.; Diniz, A.C.; Silva, A.C.; Kaiss, J.; Petzl-Erler, M.L.; Chautard-Freire-Maia, E.A. Studies on a heterologous complex formed by human butyrylcholinesterase. Biochem. Genet. 2003, 41, 141–150.

[13] Masson, P. A naturally occurring molecular form of human plasma cholinesterase is an albumin conjugate. Biochim. Biophys. Acta 1989, 998, 258–266.

[14] Sugimori, T. Shortened action of succinylcholine in individuals with cholinesterase C5 isozyme. Can. Anaesth. Soc. J. 1986, 33, 321–327.

[15] Chautard-Freire-Maia, E.A.; Primo-Parmo, S.L.; Picheth, G.; Lourenco, M.A.; Vieira, M.M. The C5 isozyme of serum cholinesterase and adult weight. Hum. Hered. 1991, 41, 330–339.

[16] Eiberg, H.; Nielsen, L.S.; Klausen, J.; Dahlen, M.; Kristensen, M.; Bisgaard, M.L.; Moller, N.; Mohr, J. Linkage between serum cholinesterase 2 (CHE2) and gamma-crystallin gene cluster (CRYG): Assignment to chromosome 2. Clin. Genet. 1989, 35, 313–321.

[17] Masson, P.; Chatonnet, A.; Lockridge, O. Evidence for a single butyrylcholinesterase gene in individuals carrying the C5 plasma cholinesterase variant (CHE2). FEBS Lett. 1990, 262, 115–118.

[18] Arpagaus, M.; Kott, M.; Vatsis, K.P.; Bartels, C.F.; La Du, B.N.; Lockridge, O. Structure of the gene for human butyrylcholinesterase. Evidence for a single copy. Biochemistry 1990, 29, 124–131.

[19] Allderdice, P.W.; Gardner, H.A.; Galutira, D.; Lockridge, O.; LaDu, B.N.; McAlpine, P.J. The cloned butyrylcholinesterase (BChE) gene maps to a single chromosome site, 3q26. Genomics 1991, 11, 452–454.

[20] Gaughan, G.; Park, H.; Priddle, J.; Craig, I.; Craig, S. Refinement of the localization of human butyrylcholinesterase to chromosome 3q26.1-q26.2 using a PCR-derived probe. Genomics 1991, 11, 455–458.

[21] Akizuki, S.; Ohnishi, A.; Kotani, K.; Sudo, K. Genetic and immunological analyses of patients with increased serum butyrylcholinesterase activity and its C5 variant form. Clin. Chem. Lab. Med. 2004, 42, 991–996.

[22] Scott, E.M.; Powers, R.F. Properties of the C5 variant form of human serum cholinesterase. Am. J. Hum. Genet. 1974, 26, 189–194.

[23] Masson, P.; Froment, M.T.; Audras, J.C.; Renault, F. Molecular characterization of the C5 human plasma cholinesterase variant. In Cholinesterases: Structure, Function, Mechanism, Genetics, and Cell, Biology, Proceedings of the Third International Meeting on Cholinesterases, La Grande-Motte, France, 12–16 May 1990; Massoulie, J., Bacou, F., Barnard, E., Chatonnet, A., Doctor, B.P., Quinn, D.M., Eds.; American Chemical Society: Washington, DC, USA, 1991; pp. 43–44, 60.

[24] Benyamin, B.; Middelberg, R.P.; Lind, P.A.; Valle, A.M.; Gordon, S.; Nyholt, D.R.; Medland, S.E.; Henders, A.K.; Heath, A.C.; Madden, P.A.; et al. GWAS of butyrylcholinesterase activity identifies four novel loci, independent effects within BChE and secondary associations with metabolic risk factors. Hum. Mol. Genet. 2011, 20, 4504–4514.

[25] De Andrade, F.A.; Batistela, M.S.; Amaral Sad, C.; Dos Santos, W.; Mikami, L.R.; Chautard-Freire-Maia, E.A.; Furtado-Alle, L.; Souza, R.L. Association between RAPH1 Gene Haplotypes and CHE2 Locus Phenotypes. Ann. Hum. Genet. 2016, 80, 203–209.

[26] Harris, H.; Hopkinson, D.A.; Robson, E.B. Two-dimensional electrophoresis of pseudocholinesterase components in normal human serum. Nature 1962, 196, 1296–1298.

[27] Yamamoto, K.; Morito, F.; Setoguchi, Y.; Fujii, S.; Kariya, T.; Sakai, T. Characterization of serum cholinesterase in familial hyper-cholinesterasemia associated with an isozyme variant band. Gastroenterol. Jpn. 1987, 22, 187–193.

[28] Deutsch, D.G.; Mertz, E.T. Plasminogen: Purification from human plasma by affinity chromatography. Science 1970, 170, 1095–1096.

[29] Pan, Y.; Muzyka, J.L.; Zhan, C.G. Model of human butyrylcholinesterase tetramer by homology modeling and dynamics simulation. J. Phys. Chem. B 2009, 113, 6543–6552.

[30] Ashton, G.C.; Simpson, N.E. C5 types of serum cholinesterase in a Brazilian population. Am. J. Hum. Genet. 1966, 18, 438–447.

[31] Whittaker, M. Cholinesterase. Monographs in Human Genetics 11: 14–15; Karger: Basel, Switzerland, 1986; Volume 11.

[32] Simon, S.; Krejci, E.; Massoulie, J. A four-to-one association between peptide motifs: Four C-terminal domains from cholinesterase assemble with one proline-rich attachment domain (PRAD) in the secretory pathway. EMBO J. 1998, 17, 6178–6187.

[33] Perrier, A.L.; Massoulie, J.; Krejci, E. PRiMA: The membrane anchor of acetylcholinesterase in the brain. Neuron 2002, 33, 275–285.

[34] Chen, V.P.; Xie, H.Q.; Chan, W.K.; Leung, K.W.; Chan, G.K.; Choi, R.C.; Bon, S.; Massoulie, J.; Tsim, K.W. The PRiMA-linked cholinesterase tetramers are assembled from homodimers: Hybrid molecules composed of acetylcholinesterase and butyrylcholinesterase dimers are up-regulated during development of chicken brain. J. Biol. Chem. 2010, 285, 27265–27278.

[35] Massoulie, J. The origin of the molecular diversity and functional anchoring of cholinesterases. Neuro-Signals 2002, 11, 130–143.

[36] Ostergaard, D.; Viby-Mogensen, J.; Hanel, H.K.; Skovgaard, L.T. Half-life of plasma cholinesterase. Acta Anaesthesiol. Scand. 1988, 32, 266–269.

[37] Karnovsky, M.J.; Roots, L. A direct-coloring thiocholine method for cholinesterases. J. Histochem. Cytochem. 1964, 12, 219–221.

[38] Ellman, G.L.; Courtney, K.D.; Andres, V., Jr.; Feather-Stone, R.M. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem. Pharmacol. 1961, 7, 88–95.

[39] Saxena, A.; Tipparaju, P.; Luo, C.; Doctor, B.P. Pilot-scale production of human serum butyrylcholinesterase suitable for use as a bioscavenger against nerve agent toxicity. Process Biochem. 2010, 45, 1313–1318.

[40] Peng, H.; Brimijoin, S.; Hrabovska, A.; Targosova, K.; Krejci, E.; Blake, T.A.; Johnson, R.C.; Masson, P.; Lockridge, O. Comparison of 5 monoclonal antibodies for immunopurification of human butyrylcholinesterase on Dynabeads: Kd values, binding pairs, and amino acid sequences. Chem. Biol. Interact. 2015, 240, 336–345.

[41] Krause, M.; Leslie, J.D.; Stewart, M.; Lafuente, E.M.; Valderrama, F.; Jagannathan, R.; Strasser, G.A.; Rubinson, D.A.; Liu, H.; Way, M.; et al. Lamellipodin, an Ena/VASP ligand, is implicated in the regulation of lamellipodial dynamics. Dev. Cell 2004, 7, 571–583.