**Supplemental Table 1**. Analyzed Tissue-specific Biomarkers with Corresponding Tissue Specificity and Function

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Biomarker Name** | **Entrez Gene Symbol** | **Literature Reference** | **Tissue Specificity Gene Enriched** | **Tissue Specificity Gene Elevated** | **Protein Function** |
| **Cardiac** | | | | | |
| Natriuretic peptides B | NPPB | McLean AS, Huang SJ, Salter M. Bench-to-bedside review: the value of cardiac biomarkers in the intensive care patient. Crit Care. 2008;12(3):215. | Yes | Yes | Cardiac hormone that plays a key role in mediating cardio-renal homeostasis |
| Myosin-binding protein C, cardiac-type | MYBPC3 | Sadayappan S, de Tombe PP. Cardiac myosin binding protein-C: redefining its structure and function. Biophys Rev. 2012;4(2):93-106. | Yes | Yes | Thick filament-associated protein located in the crossbridge region of vertebrate striated muscle a bands. In vitro it binds MHC, F-actin and native thin filaments, and modifies the activity of actin-activated myosin ATPase. It may modulate muscle contraction or may play a more structural role |
| Myoglobin | MB | Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. Indian J Cardiovasc Dis Women WINCARS. 2018;3(4):240-4. | No | Yes | Serves as a reserve supply of oxygen and facilitates the movement of oxygen within muscles. |
| Fatty acid-binding protein, heart | FABP3 | Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. Indian J Cardiovasc Dis Women WINCARS. 2018;3(4):240-4.  McLean AS, Huang SJ, Salter M. Bench-to-bedside review: the value of cardiac biomarkers in the intensive care patient. Crit Care. 2008;12(3):215. | No | Yes | FABP are thought to play a role in the intracellular transport of long-chain fatty acids and their acyl-CoA esters. |
| Troponin T, cardiac muscle | TNNT2 | Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. Indian J Cardiovasc Dis Women WINCARS. 2018;3(4):240-4. | Yes | Yes | Troponin T is the tropomyosin-binding subunit of troponin, the thin filament regulatory complex which confers calcium-sensitivity to striated muscle actomyosin ATPase activity. |
| Troponin I, cardiac muscle | TNNI3 | Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. Indian J Cardiovasc Dis Women WINCARS. 2018;3(4):240-4. | Yes | Yes | Troponin I is the inhibitory subunit of troponin, the thin filament regulatory complex which confers calcium-sensitivity to striated muscle actomyosin ATPase activity. |
| Atrial natriuretic factor | NPPA | Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. Indian J Cardiovasc Dis Women WINCARS. 2018;3(4):240-4. | Yes | Yes | Hormone that plays a key role in mediating cardio-renal homeostasis, and is involved in vascular remodeling and regulating energy metabolism |
| Brain natriuretic peptide 32 | NPPB | Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. Indian J Cardiovasc Dis Women WINCARS. 2018;3(4):240-4. | Yes | Yes | Cardiac hormone that plays a key role in mediating cardio-renal homeostasis |
| **Renal** | | | | | |
| N(G),N(G)-dimethylarginine dimethylaminohydrolase 1 | DDAH1 | Tomlinson JA, Caplin B, Boruc O, Bruce-Cobbold C, Cutillas P, Dormann D, et al. Reduced Renal Methylarginine Metabolism Protects against Progressive Kidney Damage. J Am Soc Nephrol. 2015;26(12):3045-59.  Caplin B, Nitsch D, Gill H, Hoefield R, Blackwell S, MacKenzie D, et al. Circulating methylarginine levels and the decline in renal function in patients with chronic kidney disease are modulated by DDAH1 polymorphisms. Kidney Int. 2010;77(5):459-67. | No | Yes | Hydrolyzes N(G),N(G)-dimethyl-L-arginine (ADMA) and N(G)- monomethyl-L-arginine (MMA) which act as inhibitors of NOS. Has therefore a role in the regulation of nitric oxide generation |
| Kidney-associated antigen 1 | KAAG1 | Van Den Eynde BJ, Gaugler B, Probst-Kepper M, Michaux L, Devuyst O, Lorge F, et al. A new antigen recognized by cytolytic T lymphocytes on a human kidney tumor results from reverse strand transcription. J Exp Med. 1999;190(12):1793-800.  O'Connell PJ, Zhang W, Menon MC, Yi Z, Schröppel B, Gallon L, et al. Biopsy transcriptome expression profiling to identify kidney transplants at risk of chronic injury: a multicentre, prospective study. The Lancet. 2016;388(10048):983-93. | No | Yes | Expressed in testis and kidney, and, at lower levels, in urinary bladder and liver. Expressed by a high proportion of tumors of various histologic origin, including melanomas, sarcomas and colorectal carcinomas |
| Glutaminase kidney isoform, mitochondrial | GLS | Li Q, Cui HH, Yang YJ, Li XD, Chen GH, Tian XQ, et al. Quantitative Proteomics Analysis of Ischemia/Reperfusion Injury-Modulated Proteins in Cardiac Microvascular Endothelial Cells and the Protective Role of Tongxinluo. Cell Physiol Biochem. 2017;41(4):1503-18. | No | Yes | Catalyzes the first reaction in the primary pathway for the renal catabolism of glutamine. Plays a role in maintaining acid-base homeostasis. Regulates the levels of the neurotransmitter glutamate, the main excitatory neurotransmitter in the brain |
| Uromodulin | UMOD | Gunasekara T, De Silva P, Herath C, Siribaddana S, Siribaddana N, Jayasumana C, et al. The Utility of Novel Renal Biomarkers in Assessment of Chronic Kidney Disease of Unknown Etiology (CKDu): A Review. Int J Environ Res Public Health. 2020;17(24). | Yes | Yes | Functions in biogenesis and organization of the apical membrane of epithelial cells of the thick ascending limb of Henle's loop (TALH), where it promotes formation of complex filamentous gel-like structure that may play a role in the water barrier permeability (Probable). May serve as a receptor for binding and endocytosis of cytokines (IL-1, IL-2) and TNF 1. Facilitates neutrophil migration across renal epithelia |
| Inositol oxygenase | MIOX | Sharma I, Deng F, Liao Y, Kanwar YS. Myo-inositol Oxygenase (MIOX) Overexpression Drives the Progression of Renal Tubulointerstitial Injury in Diabetes. Diabetes. 2020;69(6):1248-63.  Deng F, Sharma I, Dai Y, Yang M, Kanwar YS. Myo-inositol oxygenase expression profile modulates pathogenic ferroptosis in the renal proximal tubule. J Clin Invest. 2019;129(11):5033-49. | Yes | Yes | This protein is involved in step 1 of the subpathway that synthesizes D-glucuronate from myo-inositol. This subpathway is part of the pathway myo-inositol degradation into D-glucuronate, which is itself part of Polyol metabolism. |
| Mitochondrial coiled-coil domain protein 1 | MCCD1 | Habuka M, Fagerberg L, Hallstrom BM, Kampf C, Edlund K, Sivertsson A, et al. The kidney transcriptome and proteome defined by transcriptomics and antibody-based profiling. PLoS One. 2014;9(12):e116125. | Yes | Yes | N/A |
| **Neurologic** | | | | | |
| Gamma-enolase | ENO2 | Vizin T, Kos J. Gamma-enolase: a well-known tumour marker, with a less-known role in cancer. Radiol Oncol. 2015;49(3):217-26.  Pavlova G, Lopatina T, Kalinina N, Rybalkina E, Parfyonova Y, Tkachuk V, et al. In vitro neuronal induction of adipose-derived stem cells and their fate after transplantation into injured mouse brain. Curr Med Chem. 2012;19(30):5170-7. | Yes | Yes | Has neurotrophic and neuroprotective properties on a broad spectrum of central nervous system (CNS) neurons. |
| Protein kinase C and casein kinase substrate in neurons protein 1 | PACSIN1 | Stejskal D, Sporova L, Svestak M, Karpisek M. Determination of serum visinin like protein-1 and its potential for the diagnosis of brain injury due to the stroke: a pilot study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2011;155(3):263-8. | Yes | Yes | Plays a role in the reorganization of the microtubule cytoskeleton via its interaction with MAPT; this decreases microtubule stability and inhibits MAPT-induced microtubule polymerization. |
| Neuronal pentraxin receptor | NPTXR | Zhao ZJ, Wei DP, Zheng RZ, Peng T, Xiao X, Li FS. The Gene Coexpression Analysis Identifies Functional Modules Dynamically Changed After Traumatic Brain Injury. Comput Math Methods Med. 2021;2021:5511598.  Yin GN, Lee HW, Cho JY, Suk K. Neuronal pentraxin receptor in cerebrospinal fluid as a potential biomarker for neurodegenerative diseases. Brain Res. 2009;1265:158-70. | Yes | Yes | May be involved in mediating uptake of synaptic material during synapse remodeling or in mediating the synaptic clustering of AMPA glutamate receptors at a subset of excitatory synapses. |
| Leucine-rich repeat transmembrane neuronal protein 1 | LRRTM1 | Beste C, Arning L, Gerding WM, Epplen JT, Mertins A, Roder MC, et al. Cognitive Control Processes and Functional Cerebral Asymmetries: Association with Variation in the Handedness-Associated Gene LRRTM1. Mol Neurobiol. 2018;55(3):2268-74. | No | Yes | Exhibits strong synaptogenic activity, restricted to excitatory presynaptic differentiation, acting at both pre- and postsynaptic level. |
| Brain acid soluble protein 1 | BASP1 | Hartl M, Puglisi K, Nist A, Raffeiner P, Bister K. The brain acid-soluble protein 1 (BASP1) interferes with the oncogenic capacity of MYC and its binding to calmodulin. Mol Oncol. 2020;14(3):625-44. | No | Yes | N/A |
| Glial fibrillary acidic protein | GFAP | Vos PE, Jacobs B, Andriessen TM, Lamers KJ, Borm GF, Beems T, et al. GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology. 2010;75(20):1786-93. | Yes | Yes | GFAP, a class-III intermediate filament, is a cell-specific marker that, during the development of the central nervous system, distinguishes astrocytes from other glial cells. |
| Brain-specific angiogenesis inhibitor 1 | ADGRB1 | Stephenson JR, Paavola KJ, Schaefer SA, Kaur B, Van Meir EG, Hall RA. Brain-specific angiogenesis inhibitor-1 signaling, regulation, and enrichment in the postsynaptic density. J Biol Chem. 2013;288(31):22248-56. | Yes | Yes | Functions in endosome to Golgi retrograde transport. In response to calcium influx, may interact with SNARE fusion receptors and membrane phospholipids to mediate endosome fusion with the trans-Golgi network. By promoting the recycling of secretory vesicle transmembrane proteins, it indirectly controls dense-core secretory vesicle biogenesis, maturation and their ability to mediate the constitutive and regulated secretion of neurotransmitters and hormones. |
| Brain-derived neurotrophic factor | BDNF | Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci. 2015;11(6):1164-78. | No | Yes | Important signaling molecule that activates signaling cascades downstream of NTRK2 1. During development, promotes the survival and differentiation of selected neuronal populations of the peripheral and central nervous systems. Participates in axonal growth, pathfinding and in the modulation of dendritic growth and morphology. Major regulator of synaptic transmission and plasticity at adult synapses in many regions of the CNS. The versatility of BDNF is emphasized by its contribution to a range of adaptive neuronal responses including long-term potentiation (LTP), long-term depression (LTD), certain forms of short-term synaptic plasticity, as well as homeostatic regulation of intrinsic neuronal excitability. |
| Brain-enriched guanylate kinase-associated protein | BEGAIN | Katano T, Fukuda M, Furue H, Yamazaki M, Abe M, Watanabe M, et al. Involvement of Brain-Enriched Guanylate Kinase-Associated Protein (BEGAIN) in Chronic Pain after Peripheral Nerve Injury. eNeuro. 2016;3(5). | No | Yes | May sustain the structure of the postsynaptic density (PSD) |
| Microtubule-associated protein tau | MAPT | Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc Natl Acad Sci U S A. 1986;83(11):4044-8. | No | Yes | Promotes microtubule assembly and stability, and might be involved in the establishment and maintenance of neuronal polarity 1. The C-terminus binds axonal microtubules while the N-terminus binds neural plasma membrane components, suggesting that tau functions as a linker protein between both 2, 3. Axonal polarity is predetermined by TAU/MAPT localization (in the neuronal cell) in the domain of the cell body defined by the centrosome. The short isoforms allow plasticity of the cytoskeleton whereas the longer isoforms may preferentially play a role in its stabilization. |
| Neuronal growth regulator 1 | NEGR1 | Yan Y, Chen L, Zhou J, Xie L. SNHG12 inhibits oxygenglucose deprivationinduced neuronal apoptosis via the miR181a5p/NEGR1 axis. Mol Med Rep. 2020;22(5):3886-94. | No | Yes | May be involved in cell-adhesion. May function as a trans-neural growth-promoting factor in regenerative axon sprouting in the mammalian brain (By similarity). |
| Leucine-rich repeat transmembrane neuronal protein 4 | LRRTM4 | de Wit J, O'Sullivan ML, Savas JN, Condomitti G, Caccese MC, Vennekens KM, et al. Unbiased discovery of glypican as a receptor for LRRTM4 in regulating excitatory synapse development. Neuron. 2013;79(4):696-711. | No | Yes | May play a role in the development and maintenance of the vertebrate nervous system. Exhibits strong synaptogenic activity, restricted to excitatory presynaptic differentiation (By similarity). |
| Neurocan core protein | NCAN | Bhattacharyya S, Zhang X, Feferman L, Johnson D, Tortella FC, Guizzetti M, et al. Decline in arylsulfatase B and Increase in chondroitin 4-sulfotransferase combine to increase chondroitin 4-sulfate in traumatic brain injury. J Neurochem. 2015;134(4):728-39. | Yes | Yes | May modulate neuronal adhesion and neurite growth during development by binding to neural cell adhesion molecules (NG-CAM and N-CAM). Chondroitin sulfate proteoglycan; binds to hyaluronic acid. |
| Myelin-oligodendrocyte glycoprotein | MOG | Labombarda F, Gonzalez SL, Lima A, Roig P, Guennoun R, Schumacher M, et al. Effects of progesterone on oligodendrocyte progenitors, oligodendrocyte transcription factors, and myelin proteins following spinal cord injury. Glia. 2009;57(8):884-97. | Yes | Yes | Mediates homophilic cell-cell adhesion (By similarity). Minor component of the myelin sheath. May be involved in completion and/or maintenance of the myelin sheath and in cell-cell communication. |
| Matrix extracellular phosphoglycoprotein | MEPE | Six N, Septier D, Chaussain-Miller C, Blacher R, DenBesten P, Goldberg M. Dentonin, a MEPE fragment, initiates pulp-healing response to injury. J Dent Res. 2007;86(8):780-5. | Yes | Yes | Brain-ion transport |
| Opalin | OPALIN | Higgins GA, Georgoff P, Nikolian V, Allyn-Feuer A, Pauls B, Higgins R, et al. Network Reconstruction Reveals that Valproic Acid Activates Neurogenic Transcriptional Programs in Adult Brain Following Traumatic Injury. Pharm Res. 2017;34(8):1658-72. | Yes | Yes | Central nervous system-specific myelin protein that increase myelin genes expression during oligodendrocyte differentiation. Promotes oligodendrocyte terminal differentiation. |
| **Hepatic** | | | | | |
| Fatty acid-binding protein, liver | FABP1 | Akbal E, Koklu S, Kocak E, Cakal B, Gunes F, Basar O, et al. Liver fatty acid-binding protein is a diagnostic marker to detect liver injury due to chronic hepatitis C infection. Arch Med Res. 2013;44(1):34-8. | No | Yes | Plays a role in lipoprotein-mediated cholesterol uptake in hepatocytes, Binds cholesterol, Binds free fatty acids and their coenzyme A derivatives, bilirubin, and some other small molecules in the cytoplasm. May be involved in intracellular lipid transport (By similarity). |
| Liver carboxylesterase 1 | CES1 | Na K, Lee EY, Lee HJ, Kim KY, Lee H, Jeong SK, et al. Human plasma carboxylesterase 1, a novel serologic biomarker candidate for hepatocellular carcinoma. Proteomics. 2009;9(16):3989-99. | Yes | Yes | Involved in the detoxification of xenobiotics and in the activation of ester and amide prodrugs 1, 2, 3, 4. Hydrolyzes aromatic and aliphatic esters, but has no catalytic activity toward amides or a fatty acyl-CoA ester 5, 6, 7, 8. Hydrolyzes the methyl ester group of cocaine to form benzoylecgonine 9. Catalyzes the transesterification of cocaine to form cocaethylene 10. Displays fatty acid ethyl ester synthase activity, catalyzing the ethyl esterification of oleic acid to ethyloleate 11. Converts monoacylglycerides to free fatty acids and glycerol. Hydrolyzes of 2-arachidonoylglycerol and prostaglandins 12. Hydrolyzes cellular cholesteryl esters to free cholesterols and promotes reverse cholesterol transport (RCT) by facilitating both the initial and final steps in the process 13, 14, 15, 16. First of all, allows free cholesterol efflux from macrophages to extracellular cholesterol acceptors and secondly, releases free cholesterol from lipoprotein-delivered cholesteryl esters in the liver for bile acid synthesis or direct secretion into the bile |
| Alanine aminotransferase 1 – ALT | GPT | McGill MR. The past and present of serum aminotransferases and the future of liver injury biomarkers. EXCLI J. 2016;15:817-28. | No | Yes | Catalyzes the reversible transamination between alanine and 2-oxoglutarate to form pyruvate and glutamate. Participates in cellular nitrogen metabolism and also in liver gluconeogenesis starting with precursors transported from skeletal muscles |
| Aspartate aminotransferase, cytoplasmic | GOT1 | McGill MR. The past and present of serum aminotransferases and the future of liver injury biomarkers. EXCLI J. 2016;15:817-28. | No | Yes | Biosynthesis of L-glutamate from L-aspartate or L-cysteine. Important regulator of levels of glutamate, the major excitatory neurotransmitter of the vertebrate central nervous system. Acts as a scavenger of glutamate in brain neuroprotection. The aspartate aminotransferase activity is involved in hepatic glucose synthesis during development and in adipocyte glyceroneogenesis. |
| Liver-expressed antimicrobial peptide 2 | LEAP2 | Howard A, Townes C, Milona P, Nile CJ, Michailidis G, Hall J. Expression and functional analyses of liver expressed antimicrobial peptide-2 (LEAP-2) variant forms in human tissues. Cell Immunol. 2010;261(2):128-33. | Yes | Yes | Has an antimicrobial activity |
| Glutamate dehydrogenase 1, mitochondrial | GLUD1 | Fu S, Wu D, Jiang W, Li J, Long J, Jia C, et al. Molecular Biomarkers in Drug-Induced Liver Injury: Challenges and Future Perspectives. Front Pharmacol. 2019;10:1667. | No | Yes | Mitochondrial glutamate dehydrogenase that catalyzes the conversion of L-glutamate into alpha-ketoglutarate. Plays a key role in glutamine anaplerosis by producing alpha-ketoglutarate, an important intermediate in the tricarboxylic acid cycle 1, 2, 3, 4. Plays a role in insulin homeostasis 5, 6. May be involved in learning and memory reactions by increasing the turnover of the excitatory neurotransmitter glutamate (By similarity). |
| Sorbitol dehydrogenase | SORD | Fu S, Wu D, Jiang W, Li J, Long J, Jia C, et al. Molecular Biomarkers in Drug-Induced Liver Injury: Challenges and Future Perspectives. Front Pharmacol. 2019;10:1667. | No | Yes | Polyol dehydrogenase that catalyzes the reversible NAD(+)- dependent oxidation of various sugar alcohols. Is mostly active with D-sorbitol (D-glucitol), L-threitol, xylitol and ribitol as substrates, leading to the C2-oxidized products D-fructose, L-erythrulose, D-xylulose, and D-ribulose, respectively 1. Is a key enzyme in the polyol pathway that interconverts glucose and fructose via sorbitol, which constitutes an important alternate route for glucose metabolism. The polyol pathway is believed to be involved in the etiology of diabetic complications, such as diabetic neuropathy and retinopathy, induced by hyperglycemia |
| **Pulmonary** | | | | | |
| Surfactant-associated protein 2 | SFTA2 | Mittal RA, Hammel M, Schwarz J, Heschl KM, Bretschneider N, Flemmer AW, et al. SFTA2--a novel secretory peptide highly expressed in the lung--is modulated by lipopolysaccharide but not hyperoxia. PLoS One. 2012;7(6):e40011. | Yes | Yes | Putative surfactant protein. |
| Advanced glycosylation end product-specific receptor, soluble | AGER | Chiappalupi S, Salvadori L, Donato R, Riuzzi F, Sorci G. Hyperactivated RAGE in Comorbidities as a Risk Factor for Severe COVID-19-The Role of RAGE-RAS Crosstalk. Biomolecules. 2021;11(6). | Yes | Yes | Mediates interactions of advanced glycosylation end products (AGE). These are nonenzymatically glycosylated proteins which accumulate in vascular tissue in aging and at an accelerated rate in diabetes. Acts as a mediator of both acute and chronic vascular inflammation in conditions such as atherosclerosis and in particular as a complication of diabetes. AGE/RAGE signaling plays an important role in regulating the production/expression of TNF-alpha, oxidative stress, and endothelial dysfunction in type 2 diabetes. Interaction with S100A12 on endothelium, mononuclear phagocytes, and lymphocytes triggers cellular activation, with generation of key proinflammatory mediators. |
| Pulmonary surfactant-associated protein D | SFTPD | King BA, Kingma PS. Surfactant protein D deficiency increases lung injury during endotoxemia. Am J Respir Cell Mol Biol. 2011;44(5):709-15.  Hartl D, Griese M. Surfactant protein D in human lung diseases. Eur J Clin Invest. 2006;36(6):423-35. | Yes | Yes | Contributes to the lung's defense against inhaled microorganisms, organic antigens and toxins. Interacts with compounds such as bacterial lipopolysaccharides, oligosaccharides and fatty acids and modulates leukocyte action in immune response. May participate in the extracellular reorganization or turnover of pulmonary surfactant. Binds strongly maltose residues and to a lesser extent other alpha-glucosyl moieties. |
| Lysosome-associated membrane glycoprotein 1 | LAMP1 | Ding D, Xu S, Zhang H, Zhao W, Zhang X, Jiang Y, et al. 3-Methyladenine and dexmedetomidine reverse lipopolysaccharide-induced acute lung injury through the inhibition of inflammation and autophagy. Exp Ther Med. 2018;15(4):3516-22. | Yes | Yes | Presents carbohydrate ligands to selectins. Also implicated in tumor cell metastasis. |