

MCM Update - July 2024: ASTN2

Terminology

- **Chiari malformation type I:** A malformation in which part of the brain bulges through a normal opening in the skull where it joins the spinal canal, putting pressure on the brain and spinal cord.
- **Chronic obstructive pulmonary disease (COPD):** A group of diseases that cause airway blockage and breathing-related problems.
- **Glioblastoma:** A type of cancer which forms from cells called astrocytes in the brain or spinal cord.
- **Astrocytes:** A type of cell in the central nervous system which play many critical roles to support neurons.

Summary

We continue to characterise lung cancer biomarkers identified in the MCM1 project. This update focuses on ASTN2, a protein involved in neuronal migration. It is expressed across several tissue types, and has been implicated in various cancers.

Background

Identifying molecular markers and their combination (signatures) enables us to detect disease earlier (diagnostic signatures) and stratify patients into subgroups based on disease progression patterns (prognostic signatures). The final group of markers helps identify which patients will benefit from specific treatment options (predictive signatures). The Mapping Cancer Markers project analyses data sets with millions of data points collected from patients with cancers to find such diagnostic, prognostic and predictive signatures.

Since November 2013, World Community Grid volunteers have donated over 905,700 CPU years to the project, helping analyse data on lung and ovarian cancer and sarcoma, much more thoroughly than otherwise possible. We are immensely grateful for this continued support.

Focusing on characterising the 26 top-scoring genes in lung cancer, we have already discussed [VAMP1](#), [FARP1](#), [GSDMB](#), [ADH6](#), [IL13RA1](#), [PCSK5](#), [TLE3](#), [HSD17B11](#), and [KLF5](#) in previous MCM updates. Here, we outline information on ASTN2.

ASTN2 Research

ASTN2 (Astrotactin-2), is a protein that mediates the recycling of ASTN1 (Astrotactin-1), which is a neuronal cell adhesion molecule. This process involves promoting ASTN1 being internalised back into the neuron, and enabling its transport throughout the neuron, during neuronal migration ([Uniprot](#)).

Given ASTN2's role in the central nervous system, it is understandable that it has been implicated in emotional and cognitive functions^[1]. Evidence suggests that ASTN2 has a role in disorders linked to the brain and cognition, such as Alzheimer's disease^[2], psychiatric disorders^[3], intellectual disability^[4], migraine susceptibility^[5], and Chiari malformation type II^[6]. That said, ASTN2 has low tissue specificity and is expressed across all tissue types examined in the [Human Protein Atlas](#). Correspondingly, ASTN2 has been implicated in kidney function^[7], endometriosis^[8], osteoarthritis^[9], cardiometabolic traits^[10,11], and chronic obstructive pulmonary disease (COPD)^[12]. Interestingly, this link to COPD is a female-specific association^[12]. The potential role of ASTN2 in COPD is noteworthy because studies have demonstrated that COPD and lung cancer are closely linked at a molecular level^[13].

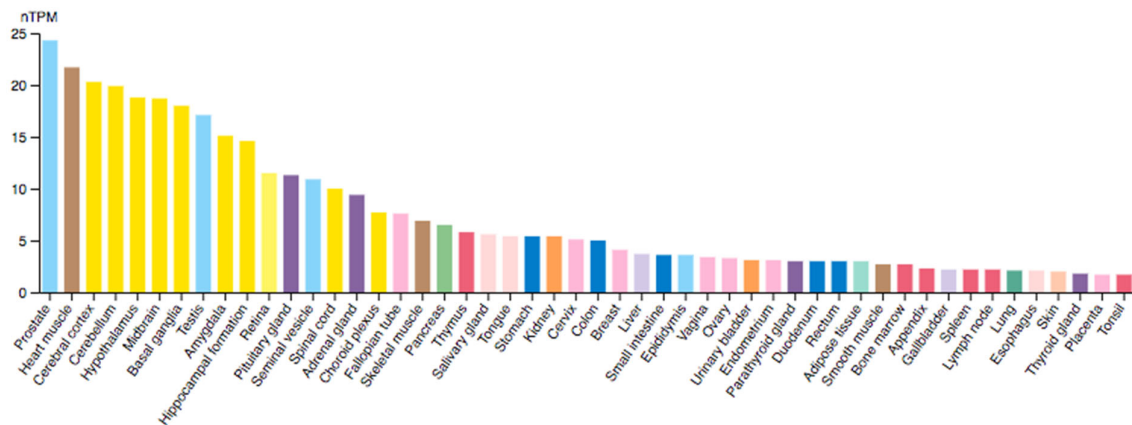


Figure 1. ASTN2 expression across different tissue types ([Human Protein Atlas](#)).

In line with the other genes we have presented, high expression of ASTN2 is associated with longer survival in lung cancer (Figure 2A). Notably, this relationship is present in females only (Figure 2B), not males (Figure 2C).

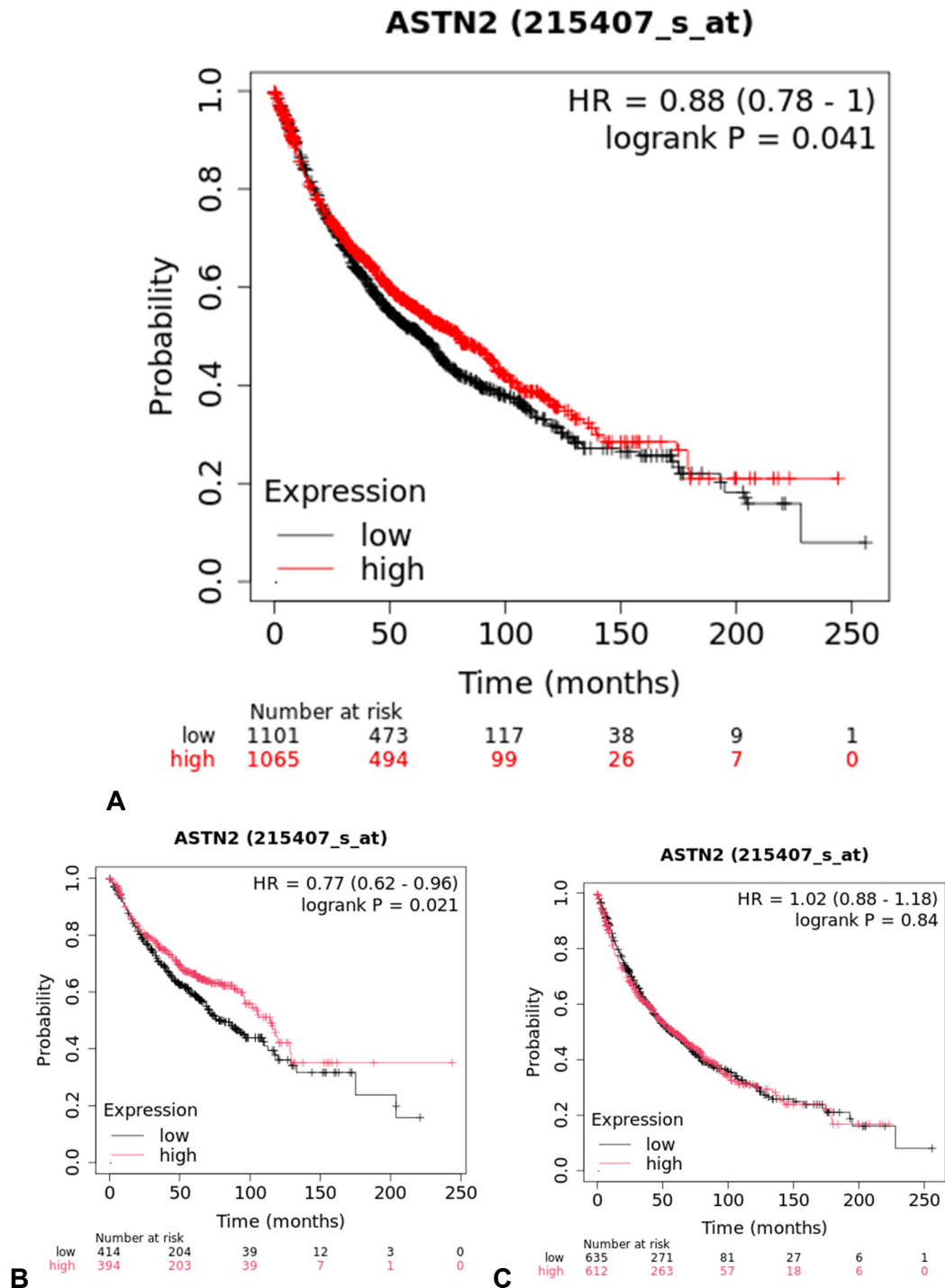


Figure 2. (A) Survival curves for lung cancer patients with low and high expression of ASTN2 ([KMplot](#)), (B) for females only, and (C) for males only.

While our focus is on lung cancer, we further examined whether ASTN2 is also linked to other cancer types. As shown in Figure 3, comparing cancer tissues with normal tissues, ASTN2 is differentially expressed in 13 of the 22 cancers analyzed (indicated by red text). Notably, ASTN2 is upregulated in 8 of these cancers, while it

is only downregulated in 5. Within the literature, the link between ASTN2 and cancer appears to be underresearched, with very few published articles on the topic. However, one study suggested that ASTN2 is linked to lung function^[14], and another study found that ASTN2 expression is elevated in glioblastoma cell lines compared with normal human astrocytes^[15].

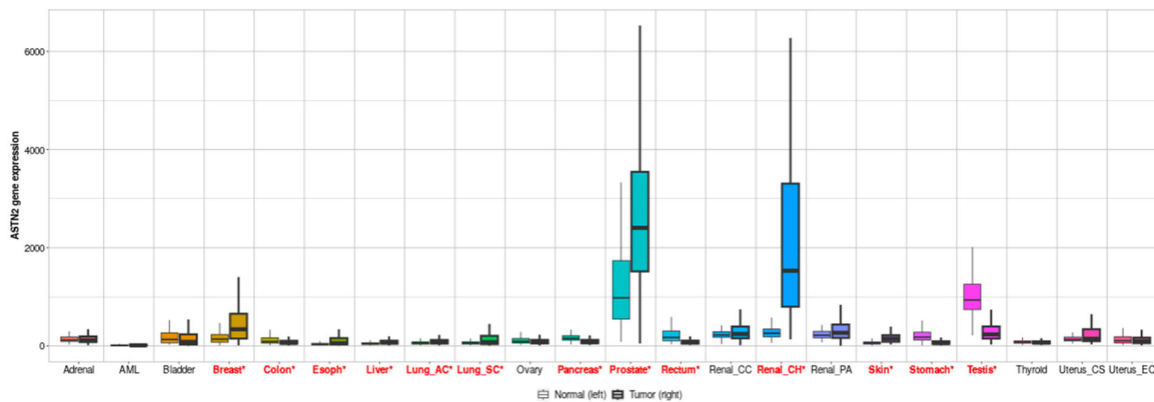


Figure 3. Expression of ASTN2 in normal and cancer tissue for multiple cancer types. Red text represents a significant difference between expression in cancer tissue compared with normal tissue ([TNMplot](#)).

If you have any questions or comments, please leave them in this thread for us to answer!

WCG Support Team

References

1. Ito T, Yoshida M, Aida T, Kushima I, Hiramatsu Y, Ono M, Yoshimi A, Tanaka K, Ozaki N, Noda Y. Astrotactin 2 (ASTN2) regulates emotional and cognitive functions by affecting neuronal morphogenesis and monoaminergic systems. *J Neurochem*. 2023 Apr;165(2):211-229. doi: 10.1111/jnc.15790. Epub 2023 Mar 15. PMID: 36807153.
2. Wang KS, Tonarelli S, Luo X, Wang L, Su B, Zuo L, Mao C, Rubin L, Briones D, Xu C. Polymorphisms within ASTN2 gene are associated with age at onset of Alzheimer's disease. *J Neural Transm (Vienna)*. 2015 May;122(5):701-8. doi: 10.1007/s00702-014-1306-z. Epub 2014 Nov 21. PMID: 25410587.
3. Pol-Fuster J, Cañellas F, Ruiz-Guerra L, Medina-Dols A, Bisbal-Carrió B, Ortega-Vila B, Llinàs J, Hernandez-Rodriguez J, Lladó J, Olmos G, Strauch K, Heine-Suñer D, Vives-Bauzá C, Flaquer A. The conserved ASTN2/BRINP1 locus at 9q33.1-33.2 is associated with major psychiatric disorders in a large pedigree from Southern Spain. *Sci Rep*. 2021 Jul 15;11(1):14529. doi: 10.1038/s41598-021-93555-4. PMID: 34267256; PMCID: PMC8282839.
4. Anazi S, Maddirevula S, Salpietro V, Asi YT, Alsahli S, Alhashem A, Shamseldin HE, AlZahrani F, Patel N, Ibrahim N, Abdulwahab FM, Hashem

- M, Alhashmi N, Al Murshedi F, Al Kindy A, Alshaer A, Rumayyan A, Al Tala S, Kurdi W, Alsaman A, Alasmari A, Banu S, Sultan T, Saleh MM, Alkuraya H, Salih MA, Aldhalaan H, Ben-Omran T, Al Musafri F, Ali R, Suleiman J, Tabarki B, El-Hattab AW, Bupp C, Alfadhel M, Al Tassan N, Monies D, Arold ST, Abouelhoda M, Lashley T, Houlden H, Faqeih E, Alkuraya FS. Expanding the genetic heterogeneity of intellectual disability. *Hum Genet.* 2017 Nov;136(11-12):1419-1429. doi: 10.1007/s00439-017-1843-2. Epub 2017 Sep 22. Erratum in: *Hum Genet.* 2018 Jan;137(1):105-109. doi: 10.1007/s00439-017-1859-7. PMID: 28940097.
5. An XK, Fang J, Yu ZZ, Lin Q, Lu CX, Qu HL, Ma QL. Multilocus analysis reveals three candidate genes for Chinese migraine susceptibility. *Clin Genet.* 2017 Aug;92(2):143-149. doi: 10.1111/cge.12962. Epub 2017 Feb 22. PMID: 28058730.
 6. AvŞar T, ÇaliŞ Ş, Yilmaz B, Demirci Otluoğlu G, Holyavkin C, Kiliç T. Genome-wide identification of Chiari malformation type I associated candidate genes and chromosomal variations. *Turk J Biol.* 2020 Dec 14;44(6):449-456. doi: 10.3906/biy-2009-19. PMID: 33402871; PMCID: PMC7759189.
 7. Gorski M, van der Most PJ, Teumer A, Chu AY, Li M, Mijatovic V, Nolte IM, Cocca M, Taliun D, Gomez F, Li Y, Tayo B, Tin A, Feitosa MF, Aspelund T, Attia J, Biffar R, Bochud M, Boerwinkle E, Borecki I, Bottinger EP, Chen MH, Chouraki V, Ciullo M, Coresh J, Cornelis MC, Curhan GC, d'Adamo AP, Dehghan A, Dengler L, Ding J, Eiriksdottir G, Endlich K, Enroth S, Esko T, Franco OH, Gasparini P, Gieger C, Girotto G, Gottesman O, Gudnason V, Gyllenstein U, Hancock SJ, Harris TB, Helmer C, Höllerer S, Hofer E, Hofman A, Holliday EG, Homuth G, Hu FB, Huth C, Hutri-Kähönen N, Hwang SJ, Imboden M, Johansson Å, Kähönen M, König W, Kramer H, Krämer BK, Kumar A, Kutalik Z, Lambert JC, Launer LJ, Lehtimäki T, de Borst M, Navis G, Swertz M, Liu Y, Lohman K, Loos RJF, Lu Y, Lyytikäinen LP, McEvoy MA, Meisinger C, Meitinger T, Metspalu A, Metzger M, Mihailov E, Mitchell P, Nauck M, Oldehinkel AJ, Olden M, Wjh Penninx B, Pistis G, Pramstaller PP, Probst-Hensch N, Raitakari OT, Rettig R, Ridker PM, Rivadeneira F, Robino A, Rosas SE, Ruderfer D, Ruggiero D, Saba Y, Sala C, Schmidt H, Schmidt R, Scott RJ, Sedaghat S, Smith AV, Sorice R, Stengel B, Stracke S, Strauch K, Toniolo D, Uitterlinden AG, Ulivi S, Viikari JS, Völker U, Vollenweider P, Völzke H, Vuckovic D, Waldenberger M, Jin Wang J, Yang Q, Chasman DI, Tromp G, Snieder H, Heid IM, Fox CS, Köttgen A, Pattaro C, Böger CA, Fuchsberger C. 1000 Genomes-based meta-analysis identifies 10 novel loci for kidney function. *Sci Rep.* 2017 Apr 28;7:45040. doi: 10.1038/srep45040. Erratum in: *Sci Rep.* 2017 May 26;7:46835. doi: 10.1038/srep46835. de Borst, Martin H [corrected to de Borst, Martin]. PMID: 28452372; PMCID: PMC5408227.
 8. Chettier R, Ward K, Albertsen HM. Endometriosis is associated with rare copy number variants. *PLoS One.* 2014 Aug 1;9(8):e103968. doi: 10.1371/journal.pone.0103968. PMID: 25083881; PMCID: PMC4118997.

9. Tyurin A, Akhilarova K, Minniakhmetov I, Mokrysheva N, Khusainova R. The Genetic Markers of Knee Osteoarthritis in Women from Russia. *Biomedicines*. 2024 Apr 2;12(4):782. doi: 10.3390/biomedicines12040782. PMID: 38672138; PMCID: PMC11048526.
10. Burt O, Johnston KJA, Graham N, Cullen B, Lyall DM, Lyall LM, Pell JP, Ward J, Smith DJ, Strawbridge RJ. Genetic Variation in the ASTN2 Locus in Cardiovascular, Metabolic and Psychiatric Traits: Evidence for Pleiotropy Rather Than Shared Biology. *Genes (Basel)*. 2021 Jul 31;12(8):1194. doi: 10.3390/genes12081194. PMID: 34440368; PMCID: PMC8391428.
11. Liu C, Zeng J, Wu J, Wang J, Wang X, Yao M, Zhang M, Fan J. Identification and validation of key genes associated with atrial fibrillation in the elderly. *Front Cardiovasc Med*. 2023 Mar 29;10:1118686. doi: 10.3389/fcvm.2023.1118686. PMID: 37063972; PMCID: PMC10090400.
12. Joo J, Himes B. Gene-Based Analysis Reveals Sex-Specific Genetic Risk Factors of COPD. *AMIA Annu Symp Proc*. 2022 Feb 21;2021:601-610. PMID: 35308900; PMCID: PMC8861659.
13. Durham AL, Adcock IM. The relationship between COPD and lung cancer. *Lung Cancer*. 2015 Nov;90(2):121-7. doi: 10.1016/j.lungcan.2015.08.017. Epub 2015 Aug 29. PMID: 26363803; PMCID: PMC4718929.
14. Soler Artigas M, Wain LV, Miller S, Kheirallah AK, Huffman JE, Ntalla I, Shrine N, Obeidat M, Trochet H, McArdle WL, Alves AC, Hui J, Zhao JH, Joshi PK, Teumer A, Albrecht E, Imboden M, Rawal R, Lopez LM, Marten J, Enroth S, Surakka I, Polasek O, Lyytikäinen LP, Granell R, Hysi PG, Flexeder C, Mahajan A, Beilby J, Bossé Y, Brandsma CA, Campbell H, Gieger C, Gläser S, González JR, Grallert H, Hammond CJ, Harris SE, Hartikainen AL, Heliövaara M, Henderson J, Hocking L, Horikoshi M, Hutri-Kähönen N, Ingelsson E, Johansson Å, Kemp JP, Kolcic I, Kumar A, Lind L, Melén E, Musk AW, Navarro P, Nickle DC, Padmanabhan S, Raitakari OT, Ried JS, Ripatti S, Schulz H, Scott RA, Sin DD, Starr JM; UK BiLEVE; Viñuela A, Völzke H, Wild SH, Wright AF, Zemunik T, Jarvis DL, Spector TD, Evans DM, Lehtimäki T, Vitart V, Kähönen M, Gyllenstein U, Rudan I, Deary IJ, Karrasch S, Probst-Hensch NM, Heinrich J, Stubbe B, Wilson JF, Wareham NJ, James AL, Morris AP, Jarvelin MR, Hayward C, Sayers I, Strachan DP, Hall IP, Tobin MD. Sixteen new lung function signals identified through 1000 Genomes Project reference panel imputation. *Nat Commun*. 2015 Dec 4;6:8658. doi: 10.1038/ncomms9658. PMID: 26635082; PMCID: PMC4686825.
15. Guo T, Bao A, Xie Y, Qiu J, Piao H. Single-Cell Sequencing Analysis Identified ASTN2 as a Migration Biomarker in Adult Glioblastoma. *Brain Sci*. 2022 Oct 30;12(11):1472. doi: 10.3390/brainsci12111472. PMID: 36358398; PMCID: PMC9688571.