

Fig. S1: Representation of functional association network of CASP2.

(<https://string-db.org/>, accessed March 2023)

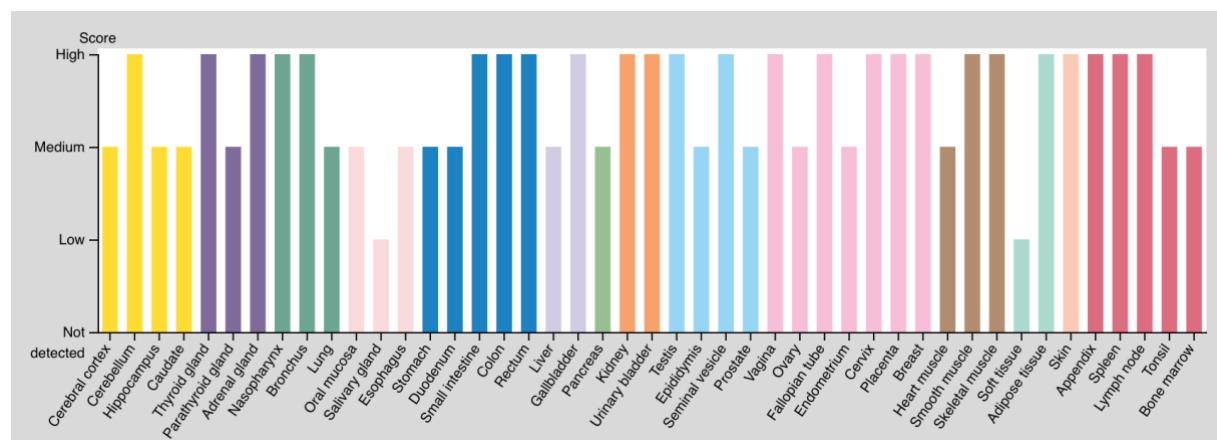


Fig. S2: CASP2 protein expression in various tissues. Protein Atlas search shows medium to high

levels of CASP2 in various organs of the human body, including brain regions

(<https://www.proteinatlas.org/>, accessed March 2023).

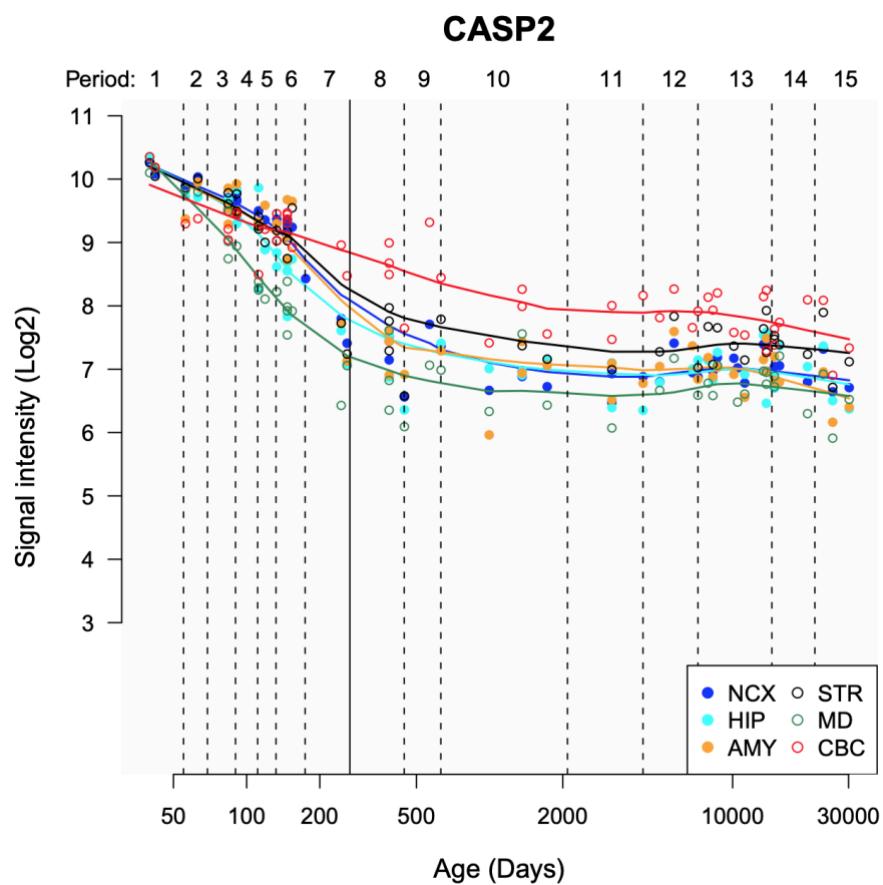


Fig. S3: Representation of dynamic CASP2 expression along entire developmental and adulthood period in the brain. The cerebellar cortex (CBC), mediiodorsal nucleus of the thalamus (MD), striatum (STR), amygdala (AMY), hippocampus (HIP) and eleven areas of neocortex (NCX) are shown. Graph generated using Human Brain Transcriptome (<https://hbatlas.org/pages/hbtd>) (accessed March 2023).

Supplementary Table 1S. List of lissencephaly related genes in the literature.

Gene	References/Year
1) <i>LIS1 (PAFAH1B1)</i>	(Reiner et al. 1993; Chong et al. 1997)
2) <i>DCX</i>	(Gleeson et al. 1998)
3) <i>RELN</i>	(Hong et al. 2000)
4) <i>ARX</i>	(Kitamura et al. 2002)
5) <i>TUBA1A</i>	(Keays et al. 2007)
6) <i>TUBB2B</i>	(Jaglin et al. 2009)
7) <i>TUBA8</i>	(Abdollahi et al. 2009)
8) <i>VLDLR</i>	(Boycott et al. 2005)
9) <i>TUBB3</i>	(Poirier et al. 2010)
10) <i>NDE1</i>	(Alkuraya et al. 2011; Bakircioglu et al. 2011)
11) <i>TUBB (TUBB5)</i>	(Breuss et al. 2012)
12) <i>ACTB</i>	(Riviere et al. 2012)
13) <i>ACTG1</i>	(Riviere et al. 2012)
14) <i>DYNC1H1</i>	(Willemsen et al. 2012)
15) <i>RNU4ATAC</i>	(Abdel-Salam et al. 2013)
16) <i>KIF2A</i>	(Poirier et al. 2013)
17) <i>KIF5C</i>	(Poirier et al. 2013)
18) <i>TUBG1</i>	(Poirier et al. 2013)
19) <i>KATNB1</i>	(Mishra-Gorur et al. 2014)
20) <i>CDK5</i>	(Magen et al. 2015)
21) <i>CRADD</i>	(Di Donato et al. 2016)
22) <i>DMRT5</i>	(Urquhart et al. 2016)
23) <i>CIT</i>	(Harding et al. 2016)
24) <i>PIDD1</i>	(Harripaul et al. 2018)
25) <i>CTNNA2</i>	(Schaffer et al. 2018)

26) <i>MACF1</i>	(Dobyns et al. 2018)
27) <i>MAST1</i>	(Tripathy et al. 2018)
28) <i>TUBGCP2</i>	(Mitani et al. 2019)
29) <i>APC2</i>	(Lee et al. 2019)
30) <i>CEP85L</i>	(Tsai et al. 2020)
31) <i>DAB1</i>	(Smits et al. 2021)

References for Supplementary Table 1.

1. Reiner O, Carrozzo R, Shen Y, Wehnert M, Faustinella F, Dobyns WB, et al. Isolation of a Miller-Dieker lissencephaly gene containing G protein beta-subunit-like repeats. *Nature*. 1993;364(6439):717-721.
2. Chong SS, Pack SD, Roschke AV, Tanigami A, Carrozzo R, Smith AC, et al. A revision of the lissencephaly and Miller-Dieker syndrome critical regions in chromosome 17p13.3. *Hum Mol Genet*. 1997;6(2):147-155.
3. Gleeson JG, Allen KM, Fox JW, Lamperti ED, Berkovic S, Scheffer I, et al. Doublecortin, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. *Cell*. 1998;92(1):63-72.
4. Hong SE, Shugart YY, Huang DT, Shahwan SA, Grant PE, Hourihane JO, et al. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. *Nat Genet*. 2000;26(1):93-96.
5. Kitamura K, Yanazawa M, Sugiyama N, Miura H, Iizuka-Kogo A, Kusaka M, et al. Mutation of ARX causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nat Genet*. 2002;32(3):359-369.
6. Keays DA, Tian G, Poirier K, Huang GJ, Siebold C, Cleak J, et al. Mutations in alpha-tubulin cause abnormal neuronal migration in mice and lissencephaly in humans. *Cell*. 2007;128(1):45-57.
7. Jaglin XH, Poirier K, Saillour Y, Buhler E, Tian G, Bahi-Buisson N, et al. Mutations in the beta-tubulin gene TUBB2B result in asymmetrical polymicrogyria. *Nat Genet*. 2009;41(6):746-752.

8. Abdollahi MR, Morrison E, Sirey T, Molnar Z, Hayward BE, Carr IM, et al. Mutation of the variant alpha-tubulin TUBA8 results in polymicrogyria with optic nerve hypoplasia. *Am J Hum Genet.* 2009;85(5):737-744.
9. Boycott KM, Flavelle S, Bureau A, Glass HC, Fujiwara TM, Wirrell E, et al. Homozygous deletion of the very low density lipoprotein receptor gene causes autosomal recessive cerebellar hypoplasia with cerebral gyral simplification. *Am J Hum Genet.* 2005;77(3):477-483.
10. Poirier K, Saillour Y, Bahi-Buisson N, Jaglin XH, Fallet-Bianco C, Nabbout R, et al. Mutations in the neuronal ss-tubulin subunit TUBB3 result in malformation of cortical development and neuronal migration defects. *Hum Mol Genet.* 2010;19(22):4462-4473.
11. Alkuraya FS, Cai X, Emery C, Mochida GH, Al-Dosari MS, Felie JM, et al. Human mutations in NDE1 cause extreme microcephaly with lissencephaly [corrected]. *Am J Hum Genet.* 2011;88(5):536-547.
12. Bakircioglu M, Carvalho OP, Khurshid M, Cox JJ, Tuysuz B, Barak T, et al. The essential role of centrosomal NDE1 in human cerebral cortex neurogenesis. *Am J Hum Genet.* 2011;88(5):523-535.
13. Breuss M, Heng JI, Poirier K, Tian G, Jaglin XH, Qu Z, et al. Mutations in the beta-tubulin gene TUBB5 cause microcephaly with structural brain abnormalities. *Cell reports.* 2012;2(6):1554-1562.
14. Riviere JB, van Bon BW, Hoischen A, Kholmanskikh SS, O'Roak BJ, Gilissen C, et al. De novo mutations in the actin genes ACTB and ACTG1 cause Baraitser-Winter syndrome. *Nat Genet.* 2012;44(4):440-444, S441-442.
15. Willemse MH, Vissers LE, Willemse MA, van Bon BW, Kroes T, de Ligt J, et al. Mutations in DYNC1H1 cause severe intellectual disability with neuronal migration defects. *J Med Genet.* 2012;49(3):179-183.
16. Abdel-Salam GM, Abdel-Hamid MS, Hassan NA, Issa MY, Effat L, Ismail S, et al. Further delineation of the clinical spectrum in RNU4ATAC related microcephalic osteodysplastic primordial dwarfism type I. *Am J Med Genet A.* 2013;161A(8):1875-1881.
17. Poirier K, Lebrun N, Broix L, Tian G, Saillour Y, Boscheron C, et al. Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nat Genet.* 2013;45(6):639-647.

18. Mishra-Gorur K, Caglayan AO, Schaffer AE, Chabu C, Henegariu O, Vonhoff F, et al. Mutations in KATNB1 cause complex cerebral malformations by disrupting asymmetrically dividing neural progenitors. *Neuron*. 2014;84(6):1226-1239.
19. Magen D, Ofir A, Berger L, Goldsher D, Eran A, Katib N, et al. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with a loss-of-function mutation in CDK5. *Hum Genet*. 2015;134(3):305-314.
20. Di Donato N, Jean YY, Maga AM, Krewson BD, Shupp AB, Avrutsky MI, et al. Mutations in CRADD Result in Reduced Caspase-2-Mediated Neuronal Apoptosis and Cause Megalencephaly with a Rare Lissencephaly Variant. *Am J Hum Genet*. 2016;99(5):1117-1129.
21. Urquhart JE, Beaman G, Byers H, Roberts NA, Chervinsky E, O'Sullivan J, et al. DMRTA2 (DMRT5) is mutated in a novel cortical brain malformation. *Clin Genet*. 2016;89(6):724-727.
22. Harding BN, Moccia A, Drunat S, Soukarieh O, Tubeuf H, Chitty LS, et al. Mutations in Citron Kinase Cause Recessive Microlissencephaly with Multinucleated Neurons. *Am J Hum Genet*. 2016;99(2):511-520.
23. Harripa R, Vasli N, Mikhailov A, Rafiq MA, Mittal K, Windpassinger C, et al. Mapping autosomal recessive intellectual disability: combined microarray and exome sequencing identifies 26 novel candidate genes in 192 consanguineous families. *Mol Psychiatry*. 2018;23(4):973-984.
24. Schaffer AE, Breuss MW, Caglayan AO, Al-Sanaa N, Al-Abdulwahed HY, Kaymakcalan H, et al. Biallelic loss of human CTNNA2, encoding alphaN-catenin, leads to ARP2/3 complex overactivity and disordered cortical neuronal migration. *Nat Genet*. 2018;50(8):1093-1101.
25. Dobyns WB, Aldinger KA, Ishak GE, Mirzaa GM, Timms AE, Grout ME, et al. MACT1 Mutations Encoding Highly Conserved Zinc-Binding Residues of the GAR Domain Cause Defects in Neuronal Migration and Axon Guidance. *Am J Hum Genet*. 2018;103(6):1009-1021.
26. Tripathy R, Leca I, van Dijk T, Weiss J, van Bon BW, Sergaki MC, et al. Mutations in MAST1 Cause Mega-Corpus-Callosum Syndrome with Cerebellar Hypoplasia and Cortical Malformations. *Neuron*. 2018;100(6):1354-1368 e1355.

27. Mitani T, Punetha J, Akalin I, Pehlivan D, Dawidziuk M, Coban Akdemir Z, et al. Bi-allelic Pathogenic Variants in TUBGCP2 Cause Microcephaly and Lissencephaly Spectrum Disorders. *Am J Hum Genet.* 2019;105(5):1005-1015.
28. Lee S, Chen DY, Zaki MS, Maroofian R, Houlden H, Di Donato N, et al. Bi-allelic Loss of Human APC2, Encoding Adenomatous Polyposis Coli Protein 2, Leads to Lissencephaly, Subcortical Heterotopia, and Global Developmental Delay. *Am J Hum Genet.* 2019;105(4):844-853.
29. Tsai MH, Muir AM, Wang WJ, Kang YN, Yang KC, Chao NH, et al. Pathogenic Variants in CEP85L Cause Sporadic and Familial Posterior Predominant Lissencephaly. *Neuron.* 2020;106(2):237-245 e238.
30. Smits DJ, Schot R, Wilke M, van Slegtenhorst M, de Wit MCY, Dremmen MHG, et al. Biallelic DAB1 Variants Are Associated With Mild Lissencephaly and Cerebellar Hypoplasia. *Neurol Genet.* 2021;7(2):e558.