

Supplementary Note 3: SNPs linked to genes that contribute broadly to brain development, patterning and plasticity

Beside *SEMA3D* and *ROBO3*, *BCAN* and *VCAN* have also been involved in axon guidance and signalling pathways in neurons¹. Similarly, a SNP in *EPHA3* was associated in our GWAS with cluster 6, which included many rfMRI functional connections between the middle temporal sulcus and mainly prefrontal and parietal brain areas (rs35124509, (missense), $p=4.49E-22$). *EPHA3* mediates the regulation of cell migration and axon guidance², and regulates trans-axonal signalling³. The other relevant findings are: one SNP is an eQTL of *WDR75*, which codes for a protein that reduces the expression of homeobox *NANOG*⁴ and was associated with T2* in the pallidum (rs6740926, $P_{\min}=1.31E-14$, cluster 5); one SNP in 3' UTR of *ZIC4*, whose loss can lead to cerebellar malformations and was associated with multiple rfMRI connections mainly between prefrontal, cerebellar and parietal areas (rs2279829, $P=8.34E-12$, cluster 8); one SNP in *ZIP8* (see main text) which plays a role in brain development via release from choroid plexus; one SNP in *NR2F1-AS1* (*COUP-TF1*), a master regulator which interacts with *PAX6* (rs7442779, $P=8.18E-15$, cluster 12); one SNP in *HBEGF* which codes for a protein that stimulates neurogenesis in proliferative zones of the adult brain (see main text); one SNP in *WNT16* (rs2908004 (missense), $P=3.5E-16$, cluster 17); one SNP in *DAAMI*, which is involved in cell polarity and which duplication is associated with cerebral palsy (rs74826997, $P=2.5E-16$, cluster 31); one SNP in *ZIP12* (see main text), whose knockdown delays neural tube closure and causes severe neural tube defects⁵; and SNPs in *EFEMP1*, *ALDH1A2* and *COASY* (see main text). Finally, another SNP in *PLCE1*, which codes for a protein that regulates various processes affecting cell growth, differentiation, and gene expression, was associated with amplitudes in various resting-state networks (top SNP rs2274224 (missense), $P=6.55E-19$, associated with the salience network, cluster 24), as well as body water composition and blood pressure in the UK Biobank participants (which can be looked up using the Oxford BIG Browser www.big.stats.ox.ac.uk) Of note, two of the SNPs in cluster 24, associated respectively with resting-state nodes in the precuneus and parietal lobule, were also found associated with migraine in 2 previous GWAS⁶ (rs11187838, $P=3.05E-15$, and rs10786156, $P=4.57E-12$).

References

1. Ohtake, Y., Wong, D., Abdul-Muneer, P. M., Selzer, M. E. & Li, S. Two PTP receptors mediate CSPG inhibition by convergent and divergent signaling pathways in neurons. *Sci Rep* **6**, srep37152 (2016).
2. Shi, G., Yue, G. & Zhou, R. EphA3 Functions are Regulated by Collaborating Phosphotyrosine Residues. *Cell research* **20**, 1263–1275 (2010).
3. Gallarda, B. W. *et al.* Segregation of Axial Motor and Sensory Pathways via Heterotypic Trans-Axonal Signaling. *Science* **320**, 233–236 (2008).
4. You, K. T., Park, J. & Kim, V. N. Role of the small subunit processome in the maintenance of pluripotent stem cells. *Genes Dev.* **29**, 2004–2009 (2015).
5. Chohanadisai, W., Graham, D. M., Keen, C. L., Rucker, R. B. & Messerli, M. A. Neurulation and neurite extension require the zinc transporter ZIP12 (slc39a12). *Proc. Natl. Acad. Sci. U.S.A.* **110**, 9903–9908 (2013).
6. Pickrell, J. K. *et al.* Detection and interpretation of shared genetic influences on 42 human traits. *Nat. Genet.* (2016). doi:10.1038/ng.3570