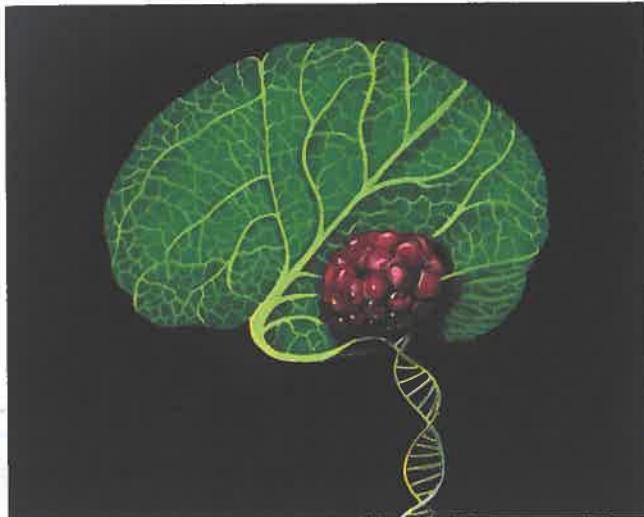


# BRAIN



**Cover image:** Cerebral and spinal cord cavernous malformations present as mulberry-like malformations of the microvasculature of the CNS. From Hong et al. Somatic MAP3K3 and PIK3CA mutations in sporadic cerebral and spinal cord cavernous malformations. Pp. 2648–2658.

## Contents

### Editorial

- The value of studying rare genetic variants and other emerging themes in neurogenetics  
B. J. Traynor and R. F. Gottesman  
2555

### Essay

- Visual agnosia and imagery after Lissauer  
P. Bartolomeo  
2557

### Scientific Commentaries

- Another step towards defining the genetic landscape of rhabdomyolysis  
G. Ravenscroft and M. Cabrera-Serrano  
2560
- Dying-back of ascending noradrenergic projections in Parkinson's disease  
R. C. Helmich and S. Lehéricy  
2562
- Towards a comprehensive 3D mapping of tau progression in early Alzheimer's disease  
A. R. Khan, J. Ottoy and M. Goubran  
2565
- Sleep and future cognitive decline  
E. Coulthard and J. Blackman  
2568

**Review Articles****The role of gut dysbiosis in Parkinson's disease: mechanistic insights and therapeutic options**

Q. Wang, Y. Luo, K. Ray Chaudhuri, R. Reynolds, E.-K. Tan and S. Pettersson

2571

**Tumour immune landscape of paediatric high-grade gliomas**

J. L. Ross, J. Velazquez Vega, A. Plant, T. J. MacDonald, O. J. Becher and D. Hambardzumyan

2594

**Update****HOPS-associated neurological disorders (HOPSANDs): linking endolysosomal dysfunction to the pathogenesis of dystonia**

E. Monfrini, M. Zech, D. Steel, M. A. Kurian, J. Winkelmann and A. Di Fonzo

2610

**Reports****Heterozygous HTRA1 nonsense or frameshift mutations are pathogenic**Heterozygous HTRA1 nonsense or frameshift mutations are pathogenic  
T. Coste, D. Hervé, J. P. Neau, E. Jouvent, F. Ba, F. Bergametti, M. Lamy, J. Cogez, N. Derache, R. Schneckenburger, M. Grelet, C. Gollion, L. Lanotte, V. Lauer, V. Layet, C. Urbanczyk, M. Didic, I. Raynouard, L. Delaval, J. Dassa, A. Florea, C. Badiu, K. Nguyen and E. Tournier-Lasserve

2616

**Classification of neurological diseases using multi-dimensional CSF analysis**Classification of neurological diseases using multi-dimensional CSF analysis  
C. C. Gross, A. Schulte-Mecklenbeck, L. Madireddy, M. Pawlitzki, C. Strippel, S. Räuber, J. Krämer, L. Rolfs, T. Ruck, C. Beuker, A. Schmidt-Pogoda, L. Lohmann, T. Schneider-Hohendorf, T. Hahn, N. Schwab, J. Minnerup, N. Melzer, L. Klotz, S. G. Meuth, G. Meyer zu Hörste, S. E. Baranzini and H. Wiendl

2625

**Clinical Trial****The unfolded protein response in amyotrophic lateral sclerosis: results of a phase 2 trial**The unfolded protein response in amyotrophic lateral sclerosis: results of a phase 2 trial  
E. Dalla Bella, E. Bersano, G. Antonini, G. Borghero, M. Capasso, C. Caponnetto, A. Chiò, M. Corbo, M. Filosto, F. Giannini, R. Spataro, C. Lunetta, J. Mandrioli, S. Messina, M. R. Monsurrò, G. Mora, N. Riva, R. Rizzi, G. Siciliano, V. Silani, I. Simone, G. Sorarù, V. Tugnoli, L. Verriello, P. Volanti, R. Furlan, J. M. Nolan, E. Abgueguen, I. Tramacere and G. Lauria

2635

**Original Articles****Somatic MAP3K3 and PIK3CA mutations in sporadic cerebral and spinal cord cavernous malformations**Somatic MAP3K3 and PIK3CA mutations in sporadic cerebral and spinal cord cavernous malformations  
T. Hong, X. Xiao, J. Ren, B. Cui, Y. Zong, J. Zou, Z. Kou, N. Jiang, G. Meng, G. Zeng, Y. Shan, H. Wu, Z. Chen, J. Liang, X. Xiao, J. Tang, Y. Wei, M. Ye, L. Sun, G. Li, P. Hu, R. Hui, H. Zhang and Y. Wang

2648

Biallelic PI4KA variants cause a novel neurodevelopmental syndrome with hypomyelinating leukodystrophy  
E. Verdura, A. Rodríguez-Palmero, V. Vélez-Santamaría, L. Planas-Serra, I. de la Calle, M. Raspall-Chaure, A. Roubertie, M. Benkirane, F. Saettini, L. Pavinato, G. Mandrile, M. O'Leary, E. O'Heir, E. Barredo, A. Chacón, V. Michaud, C. Goizet, M. Ruiz, A. Schlüter, I. Rouvet, J. Sala-Coromina, C. Fossati, M. Iascone, F. Canonico, A. Marcé-Grau, P. de Souza, D. R. Adams, C. Casasnovas, H. L. Rehm, H. C. Mefford, L. González Gutierrez-Solana, A. Brusco, M. Koenig, A. Macaya and A. Pujol

2659

**Whole-exome sequencing reveals a role of HTRA1 and EGFL8 in brain white matter hyperintensities**Whole-exome sequencing reveals a role of HTRA1 and EGFL8 in brain white matter hyperintensities  
R. Malik, N. Beaufort, S. Frerich, B. Gesierich, M. K. Georgakis, K. Rannikmäe, A. C. Ferguson, C. Haffner, M. Traylor, M. Ehrmann, C. L. M. Sudlow and M. Dichgans

2670

**TSPO PET imaging of natalizumab-associated progressive multifocal leukoencephalopathy**TSPO PET imaging of natalizumab-associated progressive multifocal leukoencephalopathy  
C. Mahler, A.-M. Schumacher, M. Unterrainer, L. Kaiser, T. Höllbacher, S. Lindner, J. Havla, B. Ertl-Wagner, M. Patzig, K. Seelos, J. Neitzel, M. Mäurer, M. Krumbholz, I. Metz, W. Brück, C. Stadelmann, D. Merkler, A. Gass, V. Milenkovic, P. Bartenstein, N. L. Albert, T. Kümpfel and M. Kerschensteiner

2683

**COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital**COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital  
K. T. Thakur, E. H. Miller, M. D. Glendinning, O. Al-Dalahmah, M. A. Banu, A. K. Boehme, A. L. Boubour, S. S. Bruce, A. M. Chong, J. Claassen, P. L. Faust, G. Hargas, R. A. Hickman, S. Jambawalikar, A. G. Khandji, C. Y. Kim, R. S. Klein, A. Lignelli-Dipple, C.-C. Lin, Y. Liu, M. L. Miller, G. Moonis, A. S. Nordvig, J. B. Overdevest, M. L. Prust, S. Przedborski, W. H. Roth, A. Soung, K. Tanji, A. F. Teich, D. Agalliu, A.-C. Uhlemann, J. E. Goldman and P. Canoll

2696

**Distinctive clinical presentation and pathogenic specificities of anti-AK5 encephalitis**Distinctive clinical presentation and pathogenic specificities of anti-AK5 encephalitis  
S. Muñiz-Castrillo, J. J. Hedou, A. Ambati, D. Jones, A. Vogrig, A.-L. Pinto, M. Benaïteau, T. de Broucker, L. Fechtenbaum, P. Labauge, M. Murnane, C. Nocon, I. Taifas, C. Vialatte de Péaille, D. Psimaras, B. Joubert, V. Dubois, V. Wucher, V. Desestret, E. Mignot and J. Honnorat

2709

- MLIP causes recessive myopathy with rhabdomyolysis, myalgia and baseline elevated serum creatine kinase**  
O. Lopes Abath Neto, L. Medne, S. Donkervoort, M. E. Rodríguez-García, V. Bolduc, Y. Hu, E. Guadagnin, A. R. Foley, J. F. Brandsema, A. M. Glanzman, G. I. Tennekoon, M. Santi, J. H. Berger, L. A. Megeney, H. Komaki, M. Inoue, F. J. Cotrina-Vinagre, A. Hernández-Lain, E. Martín-Hernández, L. Williams, S. Borell, D. Schorling, K. Lin, K. Kolokotronis, U. Lichter-Konecki, J. Kirschner, I. Nishino, B. Banwell, F. Martínez-Azorín, P. G. Burgon and C. G. Bönnemann  
**2722**
- Regional locus coeruleus degeneration is uncoupled from noradrenergic terminal loss in Parkinson's disease**  
C. E. J. Doppler, M. B. Kinnerup, C. Brune, E. Farrher, M. Betts, T. D. Fedorova, J. L. Schaldemose, K. Knudsen, R. Ismail, A. D. Seger, A. K. Hansen, K. Stær, G. R. Fink, D. J. Brooks, A. Nahimi, P. Borghammer and M. Sommerauer  
**2732**
- An in vivo *Caenorhabditis elegans* model for therapeutic research in human prion diseases**  
N. Bizat, V. Parrales, S. Laoues, S. Normant, E. Levavasseur, J. Roussel, N. Privat, A. Gougerot, P. Ravassard, P. Beaudry, J.-P. Brandel, J.-L. Laplanche and S. Haïk  
**2745**
- Amyloid- $\beta$  toxicity modulates tau phosphorylation through the PAX6 signalling pathway**  
Y. Zhang, Y. Zhang, Y. Aman, C. T. Ng, W.-H. Chau, Z. Zhang, M. Yue, C. Bohm, Y. Jia, S. Li, Q. Yuan, J. Griffin, K. Chiu, D. S. M. Wong, B. Wang, D. Jin, E. Rogaeva, P. E. Fraser, E. F. Fang, P. St George-Hyslop and Y.-Q. Song  
**2759**
- Early stages of tau pathology and its associations with functional connectivity, atrophy and memory**  
D. Berron, J. W. Vogel, P. S. Insel, J. B. Pereira, L. Xie, L. E. M. Wisse, P. A. Yushkevich, S. Palmqvist, N. Mattsson-Carlgren, E. Stomrud, R. Smith, O. Strandberg and O. Hansson  
**2771**
- Three-dimensional mapping of neurofibrillary tangle burden in the human medial temporal lobe**  
P. A. Yushkevich, M. Muñoz López, M. M. Iñiguez de Onzoño Martin, R. Ittyerah, S. Lim, S. Ravikumar, M. L. Bedard, S. Pickup, W. Liu, J. Wang, L. Y. Hung, J. Lasserve, N. Vergnet, L. Xie, M. Dong, S. Cui, L. McCollum, J. L. Robinson, T. Schuck, R. de Flores, M. Grossman, M. D. Tisdall, K. Prabhakaran, G. Mizsei, S. R. Das, E. Artacho-Pérula, M. del Mar Arroyo Jiménez, M. P. Marcos Raba, F. J. Molina Romero, S. Cebada Sánchez, J. C. Delgado González, C. de la Rosa-Prieto, M. Córcoles Parada, E. B. Lee, J. Q. Trojanowski, D. T. Ohm, L. E. M. Wisse, D. A. Wolk, D. J. Irwin and R. Insua  
**2784**
- SLTRK2, an X-linked modifier of the age at onset in C9orf72 frontotemporal lobar degeneration**  
M. Barbier, A. Camuzat, K. E. Hachimi, J. Guegan, D. Rinaldi, S. Lattante, M. Houot, R. Sánchez-Valle, M. Sabatelli, A. Antonell, L. Molina-Porcel, F. Clot, P. Couratier, E. van der Ende, J. van der Zee, C. Manzoni, W. Camu, C. Cazeneuve, F. Sellal, M. Didic, V. Golfier, F. Pasquier, C. Duyckaerts, G. Rossi, A. C. Bruni, V. Alvarez, E. Gómez-Tortosa, A. de Mendonça, C. Graff, M. Masellis, B. Nacmias, B. M. Oumoussa, L. Jornea, S. Forlani, The French clinical and genetic Research network on FTLD/FTLD-ALS and PREVDEMALS, The International Frontotemporal Dementia Genomics Consortium, The European Early Onset Dementia (EU -EOD) Consortium, Brainbank Neuro-CEB Neuropathology Network, Neurological Tissue Bank of the Biobank Hospital Clinic-IDIBAPS, V. Van Deerlin, J. D. Rohrer, E. Gelpi, R. Rademakers, J. Van Swieten, E. Le Guen, C. Van Broeckhoven, R. Ferrari, E. Génin, A. Brice and I. Le Ber  
**2798**
- A passive and objective measure of recognition memory in Alzheimer's disease using Fastball memory assessment**  
G. Stothart, L. J. Smith, A. Milton and E. Coulthard  
**2812**
- Plasma markers predict changes in amyloid, tau, atrophy and cognition in non-demented subjects**  
J. B. Pereira, S. Janelidze, E. Stomrud, S. Palmqvist, D. van Westen, J. L. Dage, N. Mattsson-Carlgren and O. Hansson  
**2826**
- Mapping autonomic, mood and cognitive effects of hypothalamic region deep brain stimulation**  
C. Neudorfer, G. J. B. Elias, M. Jakobs, A. Boutet, J. Germann, K. Narang, A. Loh, M. Paff, A. Horn, W. Kucharczyk, W. Deeb, B. Salvato, L. Almeida, K. D. Foote, P. B. Rosenberg, D. F. Tang-Wai, W. S. Anderson, Z. Mari, F. A. Ponce, D. A. Wolk, A. D. Burke, S. Salloway, M. N. Sabbagh, M. M. Chakravarty, G. S. Smith, C. G. Lyketsos, M. S. Okun and A. M. Lozano  
**2837**
- Sleep and longitudinal cognitive performance in preclinical and early symptomatic Alzheimer's disease**  
B. P. Lucey, J. Wisch, A. H. Boerwinkle, E. C. Landsness, C. D. Toedebusch, J. S. McLeland, O. H. Butt, J. Hassenstab, J. C. Morris, B. M. Ances and D. M. Holtzman  
**2852**
- Kcnq2/Kv7.2 controls the threshold and bi-hemispheric symmetry of cortical spreading depolarization**  
I. Aiba and J. L. Noebels  
**2863**
- Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants**  
J. D. Symonds, K. S. Elliott, J. Shetty, M. Armstrong, A. Brunklaus, I. Cutcutache, L. A. Diver, L. Dorris, S. Gardiner, A. Jollands, S. Joss, M. Kirkpatrick, A. McLellan, S. MacLeod, M. O'Regan, M. Page, E. Pilley, D. T. Pilz, E. Stephen, K. Stewart, H. Ashrafian, J. C. Knight and S. M. Zuberi  
**2879**
- Book Review**  
**Senior moments**  
A. J. Lees  
**2892**

**Letters to the Editor**

**MATR3 haploinsufficiency and early-onset neurodegeneration**

M. Zech, A. Seibt, B. Zumbaum, D. Klee, T. Meitinger, J. Winkelmann, E. Mayatepek, M. Wagner and F. Distelmaier  
e72

**Reply: Functional cognitive disorder: dementia's blind spot**

H. A. Ball, L. McWhirter, C. Ballard, R. Bhome, D. J. Blackburn, M. J. Edwards, N. C. Fox, R. Howard, J. Huntley, J. D. Isaacs, A. J. Larner, T. R. Nicholson, C. M. Pennington, N. Poole, G. Price, J. P. Price, M. Reuber, C. Ritchie, M. N. Rossor, J. M. Schott, A. Venneri, J. Stone and A. J. Carson

e73

**Myopathic mitochondrial DNA depletion syndrome associated with biallelic variants in LIG3**

F. Invernizzi, A. Legati, A. Nasca, E. Lamantea, B. Garavaglia, M. Gusic, R. Kopajtich, H. Prokisch, M. Zeviani, C. Lamperti and D. Ghezzi

e74

**Looking beyond indirect lesion network mapping of prosopagnosia: direct measures required**

M. A. Bobes, J. Van den Stock, M. Zhan, M. Valdes-Sosa and B. de Gelder

e75

**Reply: Looking beyond indirect lesion network mapping of prosopagnosia: direct measures required**

A. L. Cohen and M. D. Fox

e76

**Errata**

e77

**Corrigenda**

e82