p-018

Thursday

Identification of common variants influencing risk of the three-repeat tauopathy Pick's disease: a genome wide association study.

William J. Scotton, Rebecca Valentino, Alejandro Martinez-Carrasco, Raquel Real, Hannah L. Macpherson, Kin Mok, Shanu F. Roemer, Rosa Rademakers, Huw R. Morris, Tammaryn Lashley, Dennis W. Dickson, Maryam Shoai, Jonathan D. Rohrer, John A. Hardy, Owen A. Ross

State of the art: Pick's disease pathology (PiD) is a rare cause of sporadic frontotemporal dementia, neuropathologically defined by the presence of Pick bodies, consisting of aggregates of 3-repeat tau (negative for 4-repeat tau). The genetic etiology of PiD remains unresolved. We assembled the Pick's disease International Consortium (PIC), to identify susceptibility loci through a genome-wide association study (GWAS).

Methodology: A logistic regression GWAS was conducted in 301 autopsy confirmed PiD cases and 1,055 controls. Lead variants were annotated using the Functional Mapping and Annotation of GWAS platform, and co-localisation analyses using the eQTLGen, PsychENCODE and METABRAIN datasets were performed. Association testing for known tauopathy risk variants was also conducted.

Results: A genome-wide significant association on chromosome 4 (4p13) (lead SNP rs112161979, P= 4.9 x 10-8, OR = 7.54 [95% CI 3.7 - 15.6]) was reported, as well as a strong association on chromosome 11 (11p15.4) (lead SNP rs7936441, P= 2.9 x 10-6, OR = 2.0 [95% CI 1.5 - 2.8]. The MAPT H2 haplotype association was confirmed (P= 0.001, OR = 1.5, [95% CI 1.2 - 2.0]). rs112161979 is an intronic SNP in the KCDT8 gene, encoding a potassium channel tetramerization domain. rs7936441, is an intronic SNP in TRIM22, encoding an E3 ubiquitin-protein ligase.

Conclusion: The PIC presents the largest cohort of autopsy confirmed PiD to date. Our GWAS provides the first evidence of genetic associations in PiD that implicate the modulation of GABAB receptor signalling via KCTD8, as well as inflammation via TRIM22, in disease pathogenesis.

Conflicts of interest

N/A