ALZHEIMER DISEASE

***BIN1* variant increases risk of Alzheimer disease through tau**

A locus upstream of the gene *BIN1* is second only to the apolipoprotein E locus as a genetic determinant of Alzheimer disease (AD) susceptibility, but the underlying mechanism has been unclear. Now, Jean-Charles Lambert and coworkers have identified an insertion allele upstream of *BIN1* that increases expression of this gene and seems to be involved in the tau pathway of AD pathology.

BIN1 is involved in numerous cellular processes, including endocytosis and regulation of cytoskeletal dynamics. “To begin to lift the veil from the role of *BIN1* in AD, we adopted a multidisciplinary approach including molecular and functional genetics, cell biology, neuropathology and *Drosophila* biology,” says Lambert.

The researchers began by measuring *BIN1* expression in human brain samples, and found increased *BIN1* transcripts in AD brains compared with brains of control individuals. Genetic analysis

of three independent AD case–control cohorts led to identification of a variant (rs59335482; an insertion of three C bases) ~28 kb upstream of *BIN1* that is associated with increased AD risk. In cell culture, this insertion allele was found to increase *BIN1* expression.

Together, the studies in humans suggested that increased expression of *BIN1* caused by the genetic variant led to increased risk of AD. To investigate the pathological underpinnings, Lambert and colleagues next turned to studies in *Drosophila*.

Neuronal overexpression of amyloid- β or tau, two key players in AD pathology, leads to rough-eye phenotype in these flies. Knockdown of *Amph*, the *Drosophila* homologue of *BIN1*, had no effect on amyloid- β -induced pathology but, importantly, ameliorated the rough-eye phenotype in tau-overexpressing flies.

To further investigate the possible interaction between *Amph* and tau in the

brain, the team focused on the mushroom bodies—part of the *Drosophila* brain that, like the hippocampus in humans, is involved in learning and memory. Tau overexpression caused ablation of mushroom bodies, but knockdown of *Amph* enabled development of this brain area, and near-normal mushroom body morphology in some flies.

Finally, reciprocal immunoprecipitation studies in human neuroblastoma cells transfected with *BIN1* and tau, and in wild-type mouse brain homogenates, suggested physical interaction between the two proteins at the physiological level.

“If confirmed, *BIN1* would be the first genetic risk factor for AD linked to the tau pathway,” says Lambert.

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Original article Chapuis, J. et al. Increased expression of *BIN1* mediates Alzheimer genetic risk by modulating tau pathology. *Mol. Psychiatry* doi:10.1038/mp.2013.1