Beyond the usual suspects: Genetic exploration of Alzheimer's disease hallmark and co-morbid neuropathological lesions

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Start Alzheimer's disease (AD) is the most common cause of dementia worldwide and although the first patient was diagnosed over 100 years ago, there is still no cure available. The lack of effective treatment options is largely due to the complexity and heterogeneity of the disease. Clinical symptoms often overlap with other types of dementia, further complicating the diagnosis and a confirmation can only be made after a post-mortem exam. Remarkably, pathological changes in the brain of AD patients can occur decades before manifestation of symptoms, offering a large window for therapeutic intervention. Identification of patients at risk or discovery of potential therapeutic targets can largely benefit from genetic investigations trying to elucidate the mechanisms behind disease pathology. Moreover, AD has a very strong genetic component with an estimated heritability of up to 70%, making the need for a better understanding of the genetic factors at play even higher.
Complexity and heterogeneity in AD are also reflected by the brain pathology. Hallmark lesions of AD are extracellular accumulations of amyloid-beta (plaques) and intracellular accumulations of hyperphosphorylated tau (tangles). These are however rarely the sole lesions that are observed. Over 60% of pathologically confirmed AD cases has co-morbid alpha-synuclein aggregates in the brain and over 90% has cerebral amyloid angiopathy (CAA), which is the accumulation of amyloid in the blood-vessel walls. Furthermore, other lesions, like pTDP-43 and granulovacuolar degeneration (GVD) can be observed as well. These lesions are not specific to AD, as they can be observed in other neurodegenerative brain diseases, but they can contribute to the disease severity and clinical profile. Large-scale genome-wide association studies (GWAS) have been the main tool in discovering genetic risk factors for AD. Over 75 loci have been associated to AD with APOE still being the strongest. However, GWAS's rely on very large sample sizes and employ clinical diagnosis of AD. Therefore, we performed a hypothesis-based analysis to map the known risk variants for AD to the different neuropathological features observed in a post-mortem cohort of 325 individuals, to better understand what the contribution to the disease profile entails. Furthermore, we performed a hypothesis-free approach where we conducted a GWAS employing specific neuropathological scores for hallmark and co-morbid lesions for 458 individuals. We discovered several genome-

wide significant signals for a variety of neuropathological phenotypes, giving us new angles to approach AD and providing new insights in the mechanisms at play.