Commentary

Benefits of Neuropsychiatric Phenomics: Example of the 5-Lipoxygenase-Leptin-Alzheimer Connection

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Phenomics is a systematic study of phenotypes on a genomewide scale that is expected to unravel, as of yet, unsuspected functional roles of the genome. It remains to be determined how to optimally approach and analyze the available phenomics databases to spearhead innovation in neuropsychiatry. By serendipitously connecting two unrelated phenotypes of increased blood levels of the adipokine leptin, a molecule that regulates appetite, in 5-lipoxygenase- (5-LOX) deficient mice and patients with a lower risk for Alzheimer’s disease (AD), we postulated a leptin-mediated basis for beneficial effects of ALOX5 (a gene encoding 5-LOX) gene-deficiency in AD. We suggest that it might be possible to avoid relying on serendipity and develop data-mining tools capable of extracting from phenomics databases indications for such novel hypotheses. Hence, we provide an example of using a free-access Arrowsmith two-node search interface to identify ALOX5 as unsuspected putative mechanisms for the previously described clinical association between increased plasma levels of leptin and a lower risk of incident dementia and AD.

A narrow definition of “phenomics” is “a systematic study of phenotypes on a genome-wide scale” [1]. Phenomics has emerged as natural result of recent successes in high-throughput genotyping. It is expected that phenomics research would unravel, as of yet, unsuspected functional roles of the genome. Notwithstanding some promise in genetic linkage studies in the fields of neurology and psychiatry, it has become a truism that neuropsychiatric disorders are too complex to be caused by a single gene disturbance.

Although new phenotypes are continuously being discovered that can be associated with neuropsychiatric disorders, it remains to be determined how to optimally approach and analyze the available phenomics databases to spearhead innovation in neuropsychiatry. Case in point is the recent report of a curious association between increased plasma levels of the adipokine leptin, a molecule that regulates appetite, and a lower risk of incident dementia and Alzheimer disease (AD) [2]. Although a number of genes have been associated with AD, no obvious genetic marker could account for the observed negative association between increased plasma leptin and AD. Finding such a marker would open novel lines of AD research.

With availability of cross-species genotype/phenotype resources such as PhenomicDB (http://www.phenomicdb.de/) one could benefit from comparisons of human phenotypes with those of experimental animal models. An obvious question arises—is there a mouse gene knockout that leads to increased plasma leptin levels and decreased AD-like pathology? It would be helpful if one could address this question in an interactive free-access phenomics database such as PhenomicDB. However, using this database we were unable to obtain a simple answer to the above hypothetical question. As it often happens, serendipity pointed us into the right direction. Through our previous research interest into links between the inflammatory enzyme 5-lipoxygenase (5-LOX) and AD [3], we were aware of a mouse knockout model in which ALOX5 gene, which encodes 5-LOX, had been made deficient. When this 5-LOX deficiency was transferred into a transgenic mouse model of AD, the Tg2576, the amyloid-β deposition in the brains of Tg2576 mice lacking 5-LOX, was reduced by 64%–80% compared with Tg2576 controls [4]. Prompted by the findings of the AD-protective phenotype of increased plasma leptin [2], we recalled that this leptin phenotype was recently described in the ALOX5 mouse knockout [5]. Thus, the same ALOX5 knockout that caused
an article, it appears that including leptin and 5-LOX in future clinical studies with this and similar AD patient populations is warranted.

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References


