Bioinformatics approach: Regulation of Alzheimer's disease-related genes by modules of TFBSs and microRNAs

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The molecular mechanisms and genetic risk factors underlying Alzheimer's disease (AD) pathogenesis are only partly understood. To identify new factors, which may contribute to AD, different approaches are taken including proteomics, genetics and functional genomics. Here, we used a bioinformatics approach and found that distinct AD-related genes share modules of transcription factor binding sites, suggesting a transcriptional coregulation.

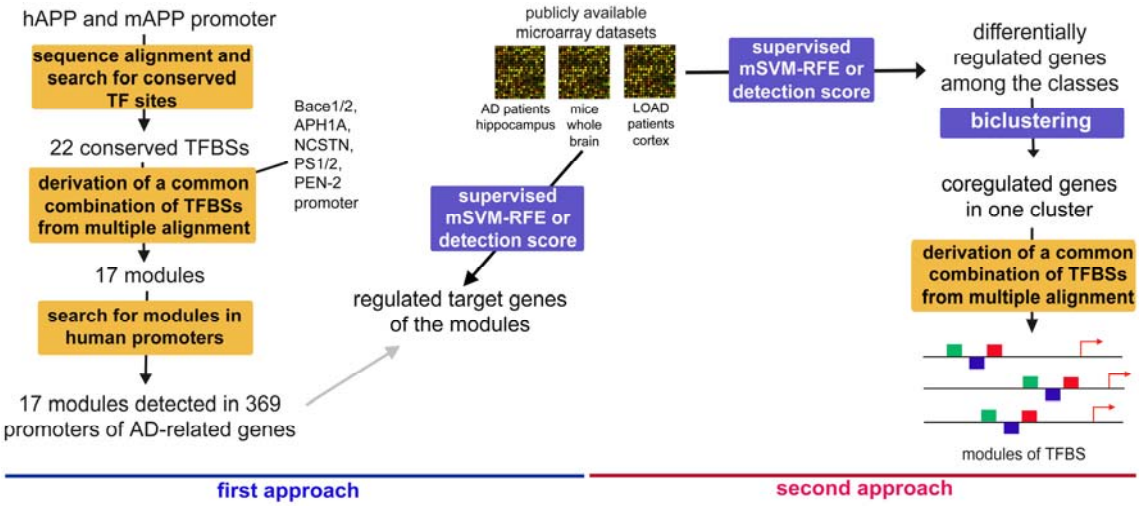

Figure 1

To detect additional coregulated genes, which may potentially contribute to AD, we established a new bioinformatics workflow (see Figure 1) with known multivariate methods [1,2], like supported vector machines, biclustering, and predicted transcription factor binding site modules by using in silico analysis [3] and over 400 expression arrays from human and mouse [4]. Two significant modules are composed of three transcription factor families CTCF, SP1F, EGRF/ZBPF (I and II in Figure 2), which are conserved between human and mouse APP promoter sequences. The specific combination of in silico promoter and multivariate analysis can identify regulation mechanisms of genes involved in multifactorial diseases. [5]

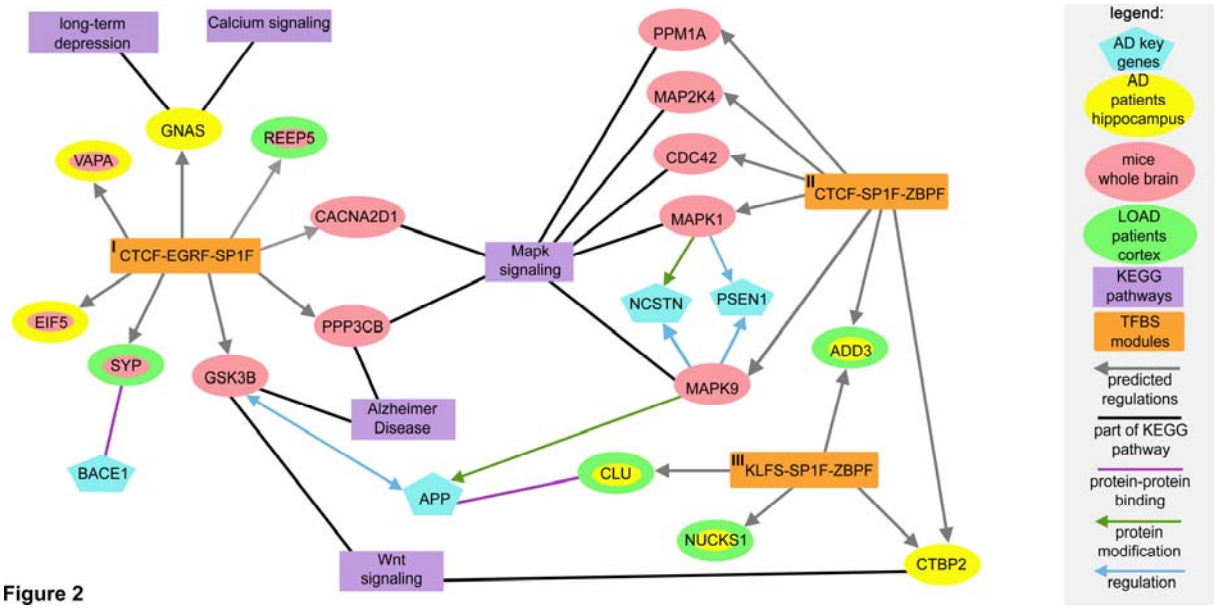

Figure 2

The aim of a second project was to find a mechanism to over express the α-secretase ADAM10 and consequently to produce more soluble sAPPα compared to neurotoxic Aβ (plaques) by computational identification of putative functional active microRNAs. With the programs RNA22, miRanda and RNAhybrid we predicted 133 microRNAs, which bind to human ADAM10. In order to strengthen the target site prediction we restricted the detected interactions to microRNAs, which are predicted to bind to human and mouse 3'UTR of ADAM10 or to multiple sites of the target gene. Furthermore, microRNAs were considered showing differential expression in AD brain regions according to Cogswell et al. (2008) or MGI database. After the filtering procedure 60 microRNAs remained. Finally, 4 different microRNA binding sites were found to be conserved across at least 8 species including the far related species zebrafish. The next step will be the validation of microRNAs in the wet-lab.

References:

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