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Transcriptomic profiling in mild cognitive impairment using peripheral blood gene co-expression networks

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Abstract

Background: In an effort towards AD prodromal risk assessment, precision medicine and biomarker development, we evaluated the efficacy of characterizing and clustering peripheral blood transcriptomic data by constructing gene-coexpression networks from differentially expressed genes between normal controls and MCI subjects.

Method: Data from the ImaGene study (Imaging and Genetics Biomarkers study of Alzheimer's Disease, ImaGene) was used. This included 160 subjects clinically diagnosed with amnestic MCI (n=70), non-amnestic MCI (n=38) and normal controls (n=52) (Table 1). Quantile-normalized and log-transformed mRNA levels were obtained from peripheral blood. In a preliminary analysis we selected 2062 genes (out of HOW MANY) which were significantly differentially expressed between normal controls and MCI (two sample t-test, $p_{fdr}<0.05$). Gene-coexpression networks were built by creating correlation matrices of the differentially expressed mRNA values. Network backbones were then built using the shortest path computation to remove redundancy and identify important edges. Hierarchical clustering was performed on the co-expression matrix to identify important communities or clusters within the network. We identified the strongest cluster associated with amnestic MCI phenotype ($p_{fdr}<0.0001$) by using the first principal component of the cluster as the eigen gene. The genes within the cluster and edges within the backbone were investigated.

Result: Upon backbone computation, the number of edges compared to original correlation matrix were significantly reduced (Figure 1). Hierarchical clustering yielded 42 clusters of genes. One cluster (eigen gene) had the strongest association with amnestic MCI phenotype ($r=0.45$, $p_{fdr}<0.0001$). This cluster consisting of 46 genes warrants further investigation for specific function and interactions with other nodes in the cluster backbone. Two of the driver genes ADRA1A and ARHGAP4 were involved in noradrenergic receptor signaling pathway and PDGF signaling pathway, both of which are dysregulated in AD pathogenesis.

Conclusion: A large noisy transcriptomic data was reduced to a critical number of mRNA measures from peripheral blood. The backbone method pruned the gene coexpression network significantly. The cluster analysis identified a set of genes which had highly significant association with amnestic MCI. This approach can also help build models for risk assessment, gene therapy and help identify novel therapeutic targets/dysregulated pathways.

Figure 1: Heatmap for original and backbone gene co-expression network ordered by cluster assignments

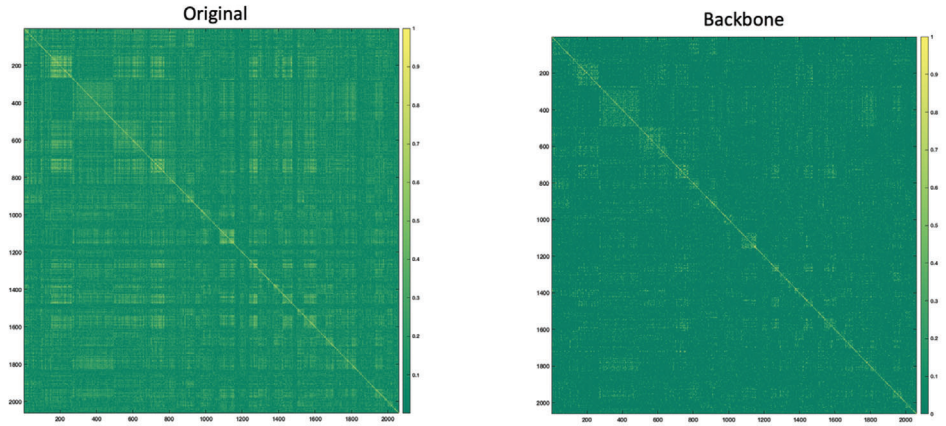

FIGURE 1

TABLE 1

Table1: ImaGene Demographics

Variable	NC	aMCI	naMCI	p-value
Mean Age(SD)	69.0(7.9)	69.3(8.5)	69.8(8.5)	0.9
Mean Education(SD)	17.6(2.0)	15.5(2.7)	16.5(2.9)	**0.001**
Gender, M/F	30/22	27/43	20/18	n.s
Mean MMSE(SD)	28.8(1.3)	27.9(2.0)	27.0(2.6)	**<0.001**
Mean Hippocampal vol(mm^3)(SD)	8600(1090)	8700(1020)	7900(1320)	**0.02**