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Identification of core subset of gene-sets associated with a continuous phenotype

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DNA microarray studies open a new platform with an opportunity to study thousands of genes at the same time. Gene-Set Analysis is a popular approach to examine the association between gene expression of a predefined gene-set and a phenotype. However, often not all the genes within a significant gene set contribute to its significance. Identifying the core subset enhances our understanding of disease biological mechanism. Many methods have been proposed for a binary outcome (diseased versus disease-free subjects), but only a few for continuous phenotype (tumor size). The challenges consist of a large number of genes in a set and a small sample size and accommodating correlations between genes across a set. We developed a powerful method to reduce the gene-sets associated with a continuous phenotype The method is based on the Linear Combination Test (LCT) for gene-sets, which incorporates the gene expression covariance matrix into the test statistic, via a shrinkage estimation approach. We applied LCT to identify significant gene-sets associated with a continuous phenotype and incorporated Significance Analysis of Microarrays to reduce them to their core subsets. We evaluated the performance of LCT-GSR in a simulation study. This methodological approach helps researchers to identify biologically meaningful genes that are mainly contributed to the association with outcome by screening massive databases, provides additional insights into disease progression and improved treatment strategies, and reduces the costs by focusing on smaller number of genes. It can be applied to a wide range of common situations in which dichotomizing the phenotype is neither easy nor meaningful.

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Identification of novel post-translational modifications in linker histones from chicken erythrocytes

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Chicken erythrocyte nuclei were digested with micrococcal nuclease and fractionated by centrifugation in low-salt buffer into soluble and insoluble fractions. Post-translational modifications of the purified linker histones of both fractions were analyzed by LC-ESI-MS/MS. All six histone H1 subtypes (H1.01, H1.02, H1.03, H1.10, H1.1L and H1.1R) and histone H5 were identified. Mass spectrometry analysis enabled the identification of a wide range of PTMs including Nα-terminal acetylation, acetylation, formylation, phosphorylation and oxidation. A total of nine new modifications in chicken linker histones were mapped, most of them located in the N-terminal and globular domains. Relative quantification of the modified peptides showed that linker histone PTMs were differentially distributed among both chromatin fractions suggesting their relevance in the regulation of chromatin structure. The analysis of our results combined with previously reported data for chicken and some mammalian species showed that most of the modified positions were conserved throughout evolution highlighting their importance in specific linker histone functions and epigenetics.

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