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Human growth is associated with distinct patterns of gene expression in evolutionarily conserved networks

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Abstract

Background: A co-ordinated tissue-independent gene expression profile associated with growth is present in rodent models and this is hypothesised to extend to all mammals. Growth in humans has similarities to other mammals but the return to active long bone growth in the pubertal growth spurt is a distinctly human growth event. The aim of this study was to describe gene expression and biological pathways associated with stages of growth in children and to assess tissue-independent expression patterns in relation to human growth.

Results: We conducted gene expression analysis on a library of datasets from normal children with age annotation, collated from the NCBI Gene Expression Omnibus (GEO) and EBI Arrayexpress databases. A primary data set was generated using cells of lymphoid origin from normal children; the expression of 688 genes (ANOVA false discovery rate modified p-value, $q < 0.1$) was associated with age, and subsets of these genes formed clusters that correlated with the phases of growth – infancy, childhood, puberty and final height. Network analysis on these clusters identified evolutionarily conserved growth pathways (NOTCH, VEGF, TGFB, WNT and glucocorticoid receptor – Hyper-geometric test, $q < 0.05$). The greatest degree of network 'connectivity' and hence functional significance was present in infancy (Wilcoxon test, $p < 0.05$), which then decreased through to adulthood. These observations were confirmed in a separate validation data set from lymphoid tissue. Similar biological pathways were observed to be associated with development-related gene expression in other tissues (conjunctival epithelia, temporal lobe brain tissue and bone marrow) suggesting the existence of a tissue-independent genetic program for human growth and maturation.

Conclusions: Similar evolutionarily conserved pathways have been associated with gene expression and child growth in multiple tissues. These expression profiles associate with the developmental phases of growth including the return to active long bone growth in puberty, a distinctly human event. These observations also have direct medical relevance to pathological changes that induce disease in children. Taking into account development-dependent gene expression profiles for normal children will be key to the appropriate selection of genes and pathways as potential biomarkers of disease or as drug targets.

Keywords: Development, Evolution, Gene expression, Growth, Network analysis, Pediatrics

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