Pathway analysis for female osteoporosis

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Osteoporosis is a prevalent bone metabolic disease characterized by bone fragility. As a key pathophysiological mechanism, the disease is caused by excessive bone resorption (by osteoclasts) over bone formation (by osteoblasts). Peripheral blood monocytes represent a major systemic cell type for bone metabolism by serving as progenitors of osteoclasts and producing cytokines important for osteoclastogenesis. To identify the key dysfunctional pathways in osteoporosis, we performed pathway analysis on microarray data of monocytes from 73 Caucasian females with extremely high or low hip BMD (bone mineral density). In current major approaches, pathways are treated as independent, but the genes overlap among them will cause “crosstalk” phenomenon and interfere the results severely. So, we firstly performed a traditional pathway analysis (Fisher’s exact test using kegg database) on our microarray data. Then we proposed a novel approach which considers the correlation among genes in the same pathway based on the real experiment data to correct the crosstalk effects in the analysis. We also applied a correction technique, MIE (maximum impact estimation) which has been reported, to our study. In traditional analysis, 10 pathways were found to be significantly associated with BMD variation. After correction by our methods, four of them (hsa05010, hsa00601, hsa01212, hsa04622) were still significant. Thus, they were considered as independent and important pathways in bone mechanism. Moreover, one pathway, MAPK signaling pathway (hsa04010) which has been proved to be important for osteoclastogenesis, became significant. Comparing with the available correction technique (MIE), all the findings in our method were biologically meaningful for osteoporosis. Because it was based on the correlation among genes in real experiment data, our method was available to reduce the false positive results and get better understanding of biological networks in the disease. In summary, we described a novel method to correct the crosstalk effect in pathway analysis and found five key independent pathways involved in BMD regulation.

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