Common middle ear diseases may affect bone behavior in the middle ear air cell system. To understand this pathologic pneumatization, the normal development of bone in the middle ear should be investigated. The objective of this study was to analyze gene expression of bone-related signaling factors and gene sets in the developing middle ear. Microarray technology was used to identify bone-related genes and gene sets, which were differentially expressed between the lining tissue of adult (quiescent) bulla and young (resorbing/forming) bulla. Data were analyzed using tools of bioinformatics and expression levels of selected genes were validated using quantitative polymerase chain reaction. The candidate gene products were compared with previously published data on middle ear bone metabolism. No differentially expressed genes were found on the outer surface of bulla. On the inner lining a total of 260 genes were identified of which 22 genes were involved in bone metabolism. Gene set analysis revealed five enriched bone-related gene sets. The identified differentially expressed bone-related mRNAs and gene sets are of potential significance in the normally developing bulla. These factors and gene sets may also play important roles during pathologic pneumatization of the middle ear air cell system in common middle ear diseases. In addition, this study suggests that the control of growth rate and wall thickness from resorptive as well as formative signals all originate from the inner lining cells of the bulla wall. Anat Rec, 297:2349–2355, 2014. © 2014 Wiley Periodicals, Inc.