A transcription factor (TF), OmpR, plays a critical role in transcriptional regulation of the osmotic stress response in bacteria. Here, we reveal a genome-scale OmpR regulon in Escherichia coli K-12 MG1655. Integrative data analysis reveals that a total of 37 genes in 24 transcription units (TUs) belong to OmpR regulon. Among them, 26 genes show more than two-fold changes in expression level in an OmpR knock-out strain. Specifically, we find that: 1) OmpR regulates mostly membrane-located gene products involved in diverse fundamental biological processes, such as narU (encoding nitrate/nitrite transporter), ompX (encoding outer membrane protein X), and nuoN (encoding NADH:ubiquinone oxidoreductase); 2) by investigating co-regulation of entire sets of genes regulated by other stressresponse TFs, stresses are surprisingly independently regulated among each other; and, 3) a detailed investigation of the physiological roles of the newly discovered OmpR regulon genes reveals that activation of narU represents a novel strategy to significantly improve osmotic stress tolerance of E. coli. Thus, the genome-scale approach to elucidating regulons comprehensively identifies regulated genes and leads to fundamental discoveries related to stress responses.