A SECOND UPDATE ON SUSCEPTIBILITY GENES FOR NICOTINE DEPENDENCE IDENTIFIED BY GENOME-WIDE LINKAGE, CANDIDATE GENE ASSOCIATION, GENOME-WIDE ASSOCIATION, AND TARGETED SEQUENCING APPROACHES

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ABSTRACT

Tobacco smoking is a severe health hazard worldwide, as nearly one-third of the global adult population smokes tobacco products, and these have been associated with numerous serious health problems. This high prevalence of tobacco use highlights the importance of studying the genetic determinants of nicotine dependence (ND). To identify genetic factors for ND, various approaches have been used, including genome-wide linkage, candidate gene-based association, genome-wide association (GWAS), and targeted sequencing analysis. In this study, we systematically analysed the findings from all the abovementioned approaches according to rigorous selection criteria for each included study such as sample size, statistical significance, and independent replication. Our analysis revealed 14 regions nominated by genome-wide linkage analysis and 34

significantly associated loci in 43 genes by candidate gene-based association. The GWAS and meta-GWAS revealed 11 genome-wide significant loci; however, only the loci on chromosomes 8, 15, and 19 have received independent replication. Although it is still in early stages, limited targeted sequencing studies using next-generation techniques have implicated 18 variants in the aetiology of ND. Together, we identified 14 linkage regions and 47 unique loci in 60 genes involved in the development of ND, which forms our current understanding of the susceptibility map for ND. Because almost all of these loci and genes have received replication by independent approaches in different samples, they should be considered high priorities for future functional study of ND.