

Evaluating Gene-Gene Interaction among Nicotine Dependence Genes on the Risk of Oral Clefts

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Abstract : Background: Maternal smoking is a recognized risk factor for nonsyndromic cleft lip with or without cleft palate (NSCL/P). It has been reported that the effect of maternal smoking on oral clefts is mediated through genes that influence nicotine dependence. The polymorphisms of cholinergic receptor nicotinic alpha (CHRNA) and beta (CHRNA) subunits genes have previously shown strong associations with nicotine dependence. Here, we attempted to investigate whether the above genes are associated with clefting risk through testing for potential gene-gene (G×G) and gene-environment (G×E) interaction. Methods: We selected 120 markers in 14 genes associated with nicotine dependence to conduct transmission disequilibrium tests among 806 Chinese NSCL/P case-parent trios ascertained in an international consortium which conducted a genome-wide association study (GWAS) of oral clefts. We applied Cordell's method using "TRIO" package in R to explore G×G as well as G×E interaction involving environmental tobacco smoke (ETS) based on conditional logistic regression model. Results: while no SNP showed significant association with NSCL/P after Bonferroni correction, we found signals for G×G interaction between 10 pairs of SNPs in CHRNA3, CHRNA5, and CHRNA4 ($p < 10^{-8}$), among which the most significant interaction was found between RS3743077 (CHRNA3) and RS11636753 (CHRNA4, $p < 8.2 \times 10^{-12}$). Linkage disequilibrium (LD) analysis revealed only low level of LD between these markers. However, there were no significant results for G×ETS interaction. Conclusion: This study fails to detect association between nicotine dependence genes and NSCL/P, but illustrates the importance of taking into account potential G×G interaction for genetic association analysis in NSCL/P. This study also suggests nicotine dependence genes should be considered as important candidate genes for NSCL/P in future studies.

Keywords : Gene-Gene Interaction, Maternal Smoking, Nicotine Dependence, Non-Syndromic Cleft Lip with or without Cleft Palate

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