Evidence for interactive effects of smoking and asthma status on associations between NOS1, NOS2A, and NOS3 genetic variants and FeNO or eosinophil levels in the EGEA study. R. Nadif\(^1\), F. Monier\(^1\), M. Boussaha\(^2\), N. Le Moual\(^1\), R. Matran\(^3\), J. Bousquet\(^1\), I. Pin\(^4\), M. Lathrop\(^5\), F. Kauffmann\(^1\), F. Demenais\(^2\), E. Bouzigon\(^2\), 1) Inserm U780, Univ Paris-Sud, IFR69, Villejuif, France; 2) Inserm, U946, Paris, France; 3) Univ Lille Nord de France, CHU, Lille, France; 4) Inserm U823, Univ Joseph Fourier, Grenoble, France; 5) CEA, CNG, Evry, France.

Asthma is a complex and heterogeneous disorder, resulting from both genetic and environmental factors. Blood eosinophil count and exhaled nitric oxide (FeNO) are markers of inflammation in asthma. Nitric oxide is produced endogenously by nitric oxide synthases (NOS). We investigated associations of FeNO level and eosinophil count with 37 tag SNPs belonging to three candidate genes: \textit{NOS1} (n=25), \textit{NOS2A} (n=5) and \textit{NOS3} (n=7), in current asthmatics and non asthmatics, and whether smoking habits modify these associations. Association analyses were conducted using GEE regression-based method in 172 families (482 adults, 39.2 yrs, 47% current asthmatics) from the French Epidemiological study on the Genetics and Environment of Asthma. Overall, FeNO levels were positively associated with asthma (geometric mean: 20.4 vs. 15.9 ppb, \(P<0.0001\)) and with eosinophil count (\(r=0.28\), \(P<0.0001\)) and negatively associated with smoking (trend \(P<0.0001\)). In asthmatics, \textit{NOS1} polymorphisms were associated with both a decreased FeNO level and an increase of eosinophil count (\(P\) ranging from 0.02 to 0.003), while no association was found in non-asthmatics (\(P_{\text{interaction}}\leq 0.03\)). Regarding FeNO level, we also found a strong interactive effect between \textit{NOS3} (rs743507) and current asthma status (\(P_{\text{interaction}}<0.0001\)). In asthmatics, TT genotype increased FeNO (29.8 vs. 19.3 ppb, \(P=0.002\)), whereas this genotype was associated with a decrease in FeNO in non-asthmatics (10.8 vs. 15.6 ppb, \(P=0.01\)). We also detected an interaction between \textit{NOS2A} polymorphisms and smoking influencing FeNO levels (\(P_{\text{interaction}}=0.002\)). Indeed, non-smithic smokers carrying AA genotype at rs3730013 had a decreased FeNO level (8.8 vs. 15.1 ppb, \(P=0.002\)), whereas no association was found in non-smokers. In asthmatics, this latter polymorphism was also associated with an increase of eosinophil count (\(P=0.002\)). No interactive effect between smoking and \textit{NOS1} or \textit{NOS3} genes on FeNO level or eosinophil count was observed. Our findings suggest that 1) associations of \textit{NOS1} and \textit{NOS3} with FeNO level and eosinophil count differed according to current asthma status and 2) smoking modify the effect of \textit{NOS2A} variants on FeNO level.

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